Risiken erkennen – Gesundheit schützen

# Variability factors for the acute dietary risk assessment of pesticides

BfR Information No 014/2010, 5 March 2010

In studies investigating the level of pesticide residues in edible commodities at harvest consequent to application of the pesticide, residues are normally not measured in single units but in composite samples consisting of several single units in order to obtain a more representative picture of the overall residue situation. Unless bulking and blending occurs before consumption (e.g. cereals), resulting in a homogeneous mixture of single units, risk assessment always needs to take into account that consumers may be exposed to one single unit with high residues. The most critical but still realistic scenario which can be imagined is the following: 1. the whole residue measured in the composite sample (e.g. 1 kg of apples) originated from one single unit (e.g. one apple) only, while all other units in the composite sample contained no residues at all, and 2. this single "high-residue apple" is then consumed. To make sure that the dietary consumer risk is not underestimated by relying on residue data for composite samples, these residue data are multiplied by a variability factor. Usually the default variability factor of 5 or 7, respectively, is used (depending on the unit weight).

Based on empiric data from unit-to-unit variability studies with pesticides, in which single units were analyzed rather than composite samples, a couple of specific variability factors were derived. They were used in the context of registration and MRL setting procedures of pesticides. These specific variability factors were in most cases between 2 and 3 and replace the default variability factor for the respective pesticide/commodity combination.

The Federal Institute for Risk Assessment (BfR) provides information on specific variability factors and discusses critically under which circumstances these factors may be used for risk assessment.

## 1 Summary

Based on empiric data from unit-to-unit variability studies a couple of variability factors, which deviate from the normally applied default values, were derived for the evaluation of supervised field trials data in the context of registration and MRL setting procedures for pesticides. In addition to these special unit-to-unit studies, market surveys were available trying to estimate the variability within lots which have probably not been subject to mixing or blending. Since the true nature of these lots is, however, unknown, they were not used to derive variability factors from.

The variability factors from supervised unit-to-unit variability studies were in most cases between 2 and 3 and were mostly derived for specific pesticide/commodity combinations. They do not necessarily apply for residues of the same pesticide in other commodities or for residues of similar pesticides in the same commodity.

It should be noted, that

- no guideline is available yet on how to conduct unit-to-unit variability studies;
- no consensus exists yet concerning the adequate accuracy of the variability factor (BfR prefers to round the values to integral numbers and use those in the assessment);
- not all of the factors mentioned herein have been confirmed on EU level and have been used to base authorization/MRL decisions on;
- the derived factors are only applicable to lots clearly identified as unblended or unmixed.

For the acute exposure assessment of market samples without clear evidence of dealing with unblended lots the default factors of 5 for units above 250 g and of 7 for units between 25 and 250 g should be applied.

## 2 Assessment

### 2.1 Introduction

Samples taken from supervised field trials are normally collected randomly and are then combined, homogenized and analyzed as a composite sample. Variability factors are used in the acute dietary intake assessment of pesticides to account for the unit-to-unit variability in composite samples, i.e. to account for the situation, in which the whole residue measured in the composite sample originated from one single unit only. Consumption of such a “high residue unit” may occur in real life and needs to be considered in risk assessment as a reasonable worst case.

### 2.2 Acute dietary intake assessment and the use of default variability factors

The acute dietary intake of pesticide residues is calculated using the so-called IESTI equation (IESTI = International Estimated Short-Term Intake). Four different versions of the equation are used for different types of commodities. Case 1 is the simple case where the residue in a composite sample reflects the residue level in a meal-sized portion of the commodity (unit weight < 25 g, i.e. cherries). Case 2 is the situation where the meal-sized portion as a single fruit or vegetable unit might have a higher residue than the composite sample. Case 2 is further divided into case 2a and case 2b where the unit size is less than or greater than the large portion size, respectively. Case 3 allows for the likely bulking and blending of processed commodities such as flour, vegetable oils and fruit juices. For more details the reader is referred to the EFSA opinion on acute dietary intake assessment (EFSA, 2007) and to the FAO manual (FAO, 2009).

The two versions of the IESTI equation in which variability factors play an important role, namely case 2a and case 2b, are depicted below:

Case 2a $$IESTI = \frac{U \times (HR\ or\ HR-P) \times \nu + (LP - U) \times (HR\ or\ HR-P)}{bw}$$

Case 2b $$IESTI = \frac{LP \times (HR\ or\ HR-P) \times \nu}{bw}$$

| | |
|---|---|
| U | Unit weight of the commodity |
| HR or HR-P | Highest residue or Highest residue after processing |
| ν | Variability factor |
| LP | Large portion |
| bw | Body weight |

According to the International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment held in York, UK (Harris et al., 2000), the variability factor is defined as the ratio between the 97.5$^{th}$ percentile and the mean of residues in individual units:

$$v = \frac{97.5th\ Percentile}{Mean}$$

In the frame of authorisation of plant protection products, the HR is estimated on the basis of supervised field residue trials in which the plants received treatments according to the most critical intended conditions of use (called “critical GAP”). As described in the introduction, composite samples of randomly selected units are usually considered to be representative of the mean residue in commodities from one treated field. To account for the theoretical 97.5$^{th}$ percentile present in the treated field and to cover a single high residue present in a single unit, the residue in the composite sample has to be multiplied with the variability factor.

Standard variability factors as included in EFSA PRIMo[1] are 5 (unit weight > 250 g) and 7 (unit weight between 25 g and 250 g). These are normally used within the EU for risk assessment and MRL setting purposes. For head lettuce and head cabbage, the standard variability factor is ambiguous. Factors 3 and 5 are currently applied. In its position paper for the 35$^{th}$ session of the CCPR in 2003 (EU Commission, 2003) the EU recommended to use a default variability factor of 3 for head lettuce and head cabbage. Consequent to this decision a factor of 3 was also used by PPR Panel in its opinion concerning the impact of a possible change of variability factors on the overall level of protection (EFSA, 2007). In the current version of EFSA PRIMo a default factor of 5 is normally pre-setted for head lettuce and head cabbage. The guidance given on notification criteria for pesticide residue findings in the RASFF system (EU Commission, 2004) is still utilizing the variability factors of 5 (unit weight > 250 g) and 7 (unit weight $\leq$ 250 g), irrespective of the commodity concerned.

It has to be noted, that the IESTI equation is currently under revision. Chapter 2.2 refers to the currently applied approach.

## 2.3 Acute dietary intake assessment and the use of specific variability factors

BfR has been provided with unit-to-unit variability studies for a couple of pesticide/commodity combinations. Some investigations were related to classes of active substances rather than to single pesticides. In addition, information is available from published literature. EFSA also reported a couple of additional data from both supervised trials and market surveys (EFSA, 2005), which have not been available to BfR and are therefore not reported herein.

The available study results are summarized in detail in the appendix to this document. All studies reported (apart from chlorpropham, which was applied post-harvest) comprise at least analyses of residues in 100 single units. Hamilton et al. (Hamilton et al., 2004) showed that a sample size of 119 or more commodity units is required to achieve a 95 % certainty that at least one unit exceeds the 97.5th percentile of the sampled population. In its opinion on appropriate variability factors (EFSA, 2005), the PPR Panel considered to take also datasets with at least 50 individual residue values into account for the estimation of the variability.

In the following table, variability factors derived from supervised unit-to-unit variability studies are summarized. If more than one study was available for one pesticide/commodity combination, the mean variability factor is given. Results from market surveys are presented in the overview table at the end of this document (appendix), but were not used to derive variability factors from.

[1] http://www.efsa.europa.eu/EFSA/General/calculation_acutechronic_rev2.xls?ssbinary=true

| Commodity | Pesticide | Variability factor |
|---|---|---|
| Apples | Azinphos-methyl | 2.4 |
| | Captan | 2.7 |
| | Dithianon | 2.9 |
| | Fenpyroxymate | 2.2 |
| | Pyraclostrobin | 2.6 |
| | Imazalil | 1.5 (post-harvest treatment only)* |
| Grapes | *Anilinopyrimidine*** | *2.6*** |
| | *Dicarboximide*** | *3.4*** |
| | *Organophosphate*** | *2.6*** |
| | Pyraclostrobin | 2.3 |
| | *Pyrethroid*** | *2.5*** |
| | *Triazole (group)*** | *2.5*** |
| Potatoes (stored) | Chlorpropham | 3.1 |
| Head cabbage | all pesticides | 3*** |
| Head lettuce | all pesticides | 3*** |

* This value is only applicable, if the treatment is known to have occurred post harvest

** One active substance from the whole group has been tested, but its identity has not been reported. It is therefore questionable, if the derived variability factor can be used for all compounds belonging to the respective group. No international agreement has been reached concerning the use of the mentioned factors. While for head cabbage and lettuce the use of an overall variability factor of 3 has been supported by JMPR and the EU Commission, this is not the case for grapes. BfR therefore does not recommend to use the mentioned factors for the time being.

*** Since only pesticide groups instead of specific pesticidal substances have been reported (see also the remark above), not the individually derived factors (< 3 each) but a slightly higher overall factor of 3 was recommended by the JMPR for head cabbage and lettuce. This accounts for uncertainties when extrapolating to all compounds belonging to the respective group.

## 2.4 Applicability of specific variability factors

The specific variability factors mentioned above have been derived for use together with supervised field trials data in the context of registration and MRL setting procedures.

Acute consumer risk assessment in the context of evaluating monitoring/surveillance samples is principally conducted as described in chapter 2.2, i.e. using the IESTI equation. The HR is, however, replaced by the OR (observed residue). OR is the residue concentration which has been measured in the respective market sample. In contrast to samples from supervised field trials, market samples often consist of different lots which have been mixed prior to marketing. This mixing may result in an increase of the variability, since treated and untreated lots may have been blended thus resulting in a lower overall mean residue while high residues on individual units remain unchanged.

In its opinion related to the appropriate variability factors to be used for acute dietary exposure assessment (EFSA, 2005), the PPR Panel confirmed that “variability factors estimated from samples collected in the marketplace were higher than those from samples obtained in experimental studies (supervised trials).” The PPR Panel therefore recommended that consideration should be given to using different variability factors when doing exposure assessments with data from supervised trials and from monitoring/surveillance. BfR and BVL have published an opinion on this issue in 2007 (Banasiak et al., 2007) and came to the conclusion that as long as standard variability factors of 5 and 7 are used in exposure assessments with data from supervised trials, the same factors may be used and are still considered protective for the assessment of monitoring/surveillance samples. As mentioned in chapter 2.2, the IESTI equation together with the variability factors in place is currently under revision.

When the revision has been finalized, the recommendation as how to use the same standard variability factors for both assessment purposes will need to be revisited.

The situation is somewhat different concerning the use of specific variability factors. As set out in chapter 2.3, these factors are usually between 2 and 3. These factors might be applied in exposure assessments with data from supervised trials. For market surveys, however, distribution ranges of variability factors were found to be much broader (EFSA, 2005). In general the BfR therefore recommends applying lowered variability factors for pesticide/commodity combinations only in those situations, where the specific lot can be clearly identified as being unblended and evenly treated over all single units. A general use of lowered variability factors might result in an underestimation of the dietary intake and is not acceptable in terms of consumer health protection.

## 3 References

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## Appendix

## Overview of unit-to-unit variability studies available to the BfR

| Commodity | Pesticide | Number of units | Estimated variability factor | Type of survey | Remarks | Reference |
|---|---|---|---|---|---|---|
| Kiwi fruit | Phosmet | 100 | 6 [a] | Market sample [c] | | Harris, C., 1998 |
| | Methidathion<br>Parathion-methyl | 100 | 5 [a]<br>2 [a] | Market sample [c] | | Harris, C., 1998 |
| | Methidathion<br>Parathion-methyl | 100 | 4 [a]<br>2 [a] | Market sample [c] | | Harris, C., 1998 |
| | Fenitrothion<br>Quinalphos | 100 | Not possible [b]<br>5 [a] | Market sample [c] | | Harris, C., 1998 |
| | Diazinon | 100 | 3 [a] | Market sample [c] | | Harris, C., 1998 |
| | **Range (total mean)** | | **2 – 6 (3.9)** | **Market sample [c]** | | |
| Plums | Chlorpyrifos<br>Pirimicarb | 100 | 6 [a]<br>Not possible [b] | Market sample [c] | | Harris, C., 1998 |
| | Chlorpyrifos<br>Phosalone | 100 | Not possible [b]<br>Not possible [b] | Market sample [c] | | Harris, C., 1998 |
| | Phosalone<br>Pirimicarb | 100 | 14 [a]<br>16 [a] | Market sample [c] | | Harris, C. 1998 |
| | Pirimicarb | 100 | 6 [a] | Market sample [c] | | Harris, C., 1998 |
| | Phosalone | 100 | 5 [a] | Market sample [c] | | Harris, C., 1998 |
| | Acephate<br>Methamidophos | 100 | 4 [a]<br>4 [a] | Market sample [c] | | Harris, C., 1998 |
| | Chlorpyrifos<br>Dimethoate<br>Omethoate | 100 | Not possible [b]<br>23 [a]<br>Not possible [b] | Market sample [c] | | Harris, C., 1998 |
| | Acephate<br>Methamidophos<br>Pirimiphos-methyl | 100 | 3 [a]<br>4 [a]<br>8 [a] | Market sample [c] | | Harris, C., 1998 |
| | Fenitrothion | 100 | 5 [a] | Market sample [c] | | Harris, C., 1998 |
| | Acephate<br>Methamidophos | 100 | 5 [a]<br>4 [a] | Market sample [c] | | Harris, C., 1998 |
| | **Range (total mean)** | | **3 – 23 (7.6)** | **Market sample [c]** | | |

| Commodity | Pesticide | Number of units | Estimated variability factor | Type of survey | Remarks | Reference |
|---|---|---|---|---|---|---|
| Apples | Dithianon | 150 | 3.8 | Supervised field trial | | Bross, M., 2006 |
| | Dithianon | 150 | 2.6 | Supervised field trial | | Bross, M., 2006 |
| | Pyraclostrobin<br>Dithianon | 150 | 2.7<br>2.4 | Supervised field trial | | Blaschke, U., 2007 |
| | Pyraclostrobin<br>Dithianon | 150 | 2.4<br>1.9 | Supervised field trial | | Blaschke, U., 2007 |
| | Pyraclostrobin<br>Dithianon | 150 | 2.7<br>3.8 | Supervised field trial | | Blaschke, U., 2007 |
| | Pyraclostrobin<br>Dithianon | 150 | 2.7<br>2.6 | Supervised field trial | | Blaschke, U., 2007 |
| | Azinphos-methyl | 100 | 2.4 | Supervised field trial | | Harrison, C., 2007 |
| | Azinphos-methyl | 100 | 2.3 | Supervised field trial | | Harrison, C., 2007a |
| | Captan | 100 | 2.7 | Supervised field trial | | Klimmek, S., 2006 |
| | Fenpyroxymate | 130 | 2.2 | Supervised field trial | | Klimmek, S., 2007 |
| | **Range (total mean)** | | **1.9-3.8 (2.7)** | **Supervised field trial** | | |
| Apples (post harvest) | Imazalil | 119 | 1.5 | Supervised post-harvest treatment | | Tetuàn, B., 2007 |
| | **Range (total mean)** | | **1.5** | **Supervised post-harvest treatment** | | |
| Grapes | Anilinopyrimidine<br>Dicarboximide<br>Organophosphate<br>Pyrethroid<br>Triazole | 120 | 2.6<br>2.9<br>2.3<br>2.6<br>3.4 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002 |
| | Anilinopyrimidine<br>Dicarboximide<br>Organophosphate<br>Pyrethroid<br>Triazole | 120 | 2.4<br>2.3<br>2.3<br>2.2<br>2.0 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002 |
| | Anilinopyrimidine<br>Dicarboximide<br>Organophosphate<br>Pyrethroid<br>Triazole | 120 | 2.5<br>2.7<br>2.5<br>2.8<br>2.4 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002 |

| Commodity | Pesticide | Number of units | Estimated variability factor | Type of survey | Remarks | Reference |
|---|---|---|---|---|---|---|
| Grapes (continued) | Anilinopyrimidine<br>Dicarboximide<br>Organophosphate<br>Pyrethroid<br>Triazole | 120 | 2.8<br>5.6<br>3.1<br>2.2<br>2.3 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002 |
| | Pyraclostrobin | 120 | 1.8 | Supervised field trial | | Heck, W., 2002 |
| | Pyraclostrobin | 120 | 2.5 | Supervised field trial | | Heck, W., 2002 |
| | Pyraclostrobin | 120 | 2.4 | Supervised field trial | | Heck, W., 2002 |
| | Pyraclostrobin | 120 | 2.4 | Supervised field trial | | Heck, W., 2002 |
| | **Range (total mean)** | | **1.8-3.4 (2.6)** | **Supervised field trial** | | |
| Potatoes | Chlorpropham | 60 | 3.1 | Supervised storage treatment | | Quirijns, J.K., 2003 |
| | **Range (total mean)** | | **3.1** | **Supervised storage treatment** | | |
| Head lettuce | Anilinopyrimidine<br>Triazole<br>Pyrethroid<br>Organophosphate<br>Dicarboximide<br>Carbamate | 120 | 2.1<br>2.0<br>1.9<br>1.6<br>1.9<br>2.0 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002a |
| | Anilinopyrimidine<br>Triazole<br>Pyrethroid<br>Organophosphate<br>Dicarboximide<br>Carbamate | 120 | 2.0<br>1.6<br>1.8<br>1.3<br>1.8<br>2.1 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002a |
| | Anilinopyrimidine<br>Triazole<br>Pyrethroid<br>Organophosphate<br>Dicarboximide<br>Carbamate | 120 | 2.2<br>1.8<br>2.2<br>2.9<br>2.5<br>1.7 | Supervised field trial | Individual compounds not specified | Kaethner, M., 2002a |

| Commodity | Pesticide | Number of units | Estimated variability factor | Type of survey | Remarks | Reference |
|---|---|---|---|---|---|---|
| Head lettuce (continued) | Anilinopyrimidine<br>Triazole<br>Pyrethroid<br>Organophosphate<br>Dicarboximide<br>Carbamate | 120 | 1.3<br>1.3<br>1.3<br>1.2<br>2.9<br>1.5 | Supervised field trial | compounds not specified | Kaethner, M., 2002a |
| | **Range (total mean)** | | **1.2-2.9 (1.9)** | **Supervised field trial** | | |

A: Based on the ratio Maximum / Mean instead of 97.5 Percentile / Mean

B: Estimation of variability factor not possible, more than 50 % of the results were < LOQ

C: Market samples described as “unblended lots”. However it is not clear, if this was really the case, so the data was not used to derive variability factors from