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Methodologies to address the succeeding crops data requirements for co-formulated plant protection products

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This document is intended to assist applicants and evaluators to interpret EPPO Standard PP1/207 Effects on succeeding crops. Expert judgement should be applied in all cases.

This paper provides guidance on assessments of succeeding crops for plant protection products containing more than one active substance. There is a need to provide clarification of this area as part of the zonal authorisation process for plant protection products (as defined in EU Regulation 1107/2009). The focus of this paper is on the initial examination of the properties of the active substances and their potential impact on succeeding crops.

Succeeding crop tests should be carried out with the formulation of the product intended for use or with the individual active substances. However, it is generally accepted that once a formulation is present in the soil then the co-formulants have no significant effect on performance (See EPPO PP 1/307). Therefore, data produced with other formulations containing the same amount of the active substance(s) are acceptable. Exceptions to this rule are where a product has been formulated in a special way that will affect the persistence of the active substance(s), e.g. slow-release granules or capsule suspensions.

Impact on succeeding crops

General information

When assessing the potential impact on succeeding crops from the proposed use of a product, a step-wise approach should be taken following EPPO Standard PP 1/207 Effects on succeeding crops, starting with the herbicidal activity of the active substance, through glasshouse screening, laboratory bio-assays of treated field soils, field screening, monitoring of effectiveness/crop safety field trials and if necessary, specific following crop 'replanting' trials using risk mitigation measures such as different cultivation techniques. It is important to consider crops which are likely to be present in crop rotations across the zone. For testing the biological activity of the test product, the product should be incorporated into the soil and the activity given as an EC (effective concentration).

The focus of this paper is on how to consider the initial examination of the properties of the active substances (section 2 of EPPO Standard PP 1/207 *Effects on succeeding crops*) for products containing more than one active substance. This includes the assessment of herbicidal activity, fate and behaviour in the soil and the need for field testing. This paper does not cover succeeding crops field trial conduct. Field trials should be carried out under Good Experimental Practice (GEP) and according to the EPPO Standard PP 1/207 *Effects on succeeding crops* (available at http://pp1.eppo.int/).
When assessing the potential impact on succeeding crops for products containing more than one active substance, there are two acceptable methods which can be followed. The first method

is to test the product in its proposed formulation, or a formulation with the same amount of the active substance(s).
The second method involves testing each individual active substance on its own at the dose that would be applied in the formulated product.
This paper covers both methods. Further guidance and details on the recommended methodologies are provided in EPPO PP 1/207.

Fate and behaviour in soil

The initial PEC (predicted environmental concentration) of the active substances in the soil ($PEC_{initial}$) can be calculated using the first equation included in EPPO PP 1/207.

The depth of the soil layer, which is determined by the cultivation method, should be considered, and the latest interception values from the FOCUS groundwater scenarios model should be used.

The second equation in EPPO PP 1/207 can be used to calculate PEC_{actual} values by using the DT_{50} of the active substances. PEC_{actual} values should be produced at a range of relevant intervals, when succeeding or replacement crops are likely to be sown.

The equations in EPPO PP 1/207 may not always be appropriate (e.g. where there is accumulation); therefore, expert fate and behaviour knowledge is required when calculating the most appropriate PEC values.

Method 1 – Formulated product risk assessment

A $PEC_{initial}$ value representing the total amount of active substance in the soil (mg ∑ a.s./kg soil) is calculated. As a worst-case scenario, PEC_{actual} values (also in mg ∑ a.s./kg soil) are then calculated using the highest DT_{50} of the active substances in the product.

Method 2 – Individual active substance(s) risk assessment

Separate $PEC_{initial}$ and PEC_{actual} values are calculated for each individual active substance in the product formulation. The relevant DT_{50} of each active substance should be used in these calculations.

Biological activity of the formulated product/active substance(s)

EC_{10} (effective concentration that causes a 10 % effect) values should normally be produced, in a suitable bioassay, for a range of representative plant species. The validity of these values may depend on the test methodology adopted.

For products with multiple active substances, it is likely that each active substance in the formulation is contributing to this negative effect on the plants. The extent to which the effect is caused by each active substance will depend on the sensitivity of each plant to each active substance, i.e. the inherent toxicity of the active substance.

In some bioassays, ER_{10}/ED_{10} values may be produced instead of EC_{10} values. Appendix 3 contains guidance on how to convert ER_{10}/ED_{10} values into EC_{10} values, which are required for calculating the TER values.

Method 1 – Formulated product risk assessment

The product is tested in a bioassay to assess its impact on a range of plants. The EC_{10} values represent the sensitivity of each plant species to the product in the soil.

As the EC_{10} value represents the sensitivity of the plant to the ratio/combination of active substances found in the product formulation, it is difficult to clearly attribute the phytotoxic effects to the single/specific active substances of the formulation.
Furthermore, the active substances will likely have different DT_{50} values and therefore, the ratio of active substances in the soil will change over time and no longer be representative of the product formulation.
Consequently, it is difficult to assess at what point it will be safe to sow succeeding crops.

Therefore, as a worst-case scenario, an EC_{10} value representing the total amount of active substance in the soil can be used (mg ∑ a.s./kg soil).

Method 2 – Individual active substance(s) risk assessment

Each active substance is tested individually in separate bioassays to assess their impact on a range of plants. The EC_{10} values represent the sensitivity of each plant species to the individual active substance in the soil.

TER calculation and deciding on the need for field testing

Using the range of PEC_{actual} values along with the EC_{10} values, it is possible to determine at what intervals after application it should be safe to sow various succeeding crops. This can be done by calculating Toxicity-Exposure Ratio (TER) values. The safe sowing intervals will depend on the EC_{10} values of the plants, the initial amount of the active substances in the soil, the DT_{50} of the active substances and the depth of soil cultivation.

$$\boldsymbol{TER = \frac{EC10}{PEC}}$$

TER values should generally be calculated at relevant intervals after application i.e. the earliest dates at which succeeding/replacement crops could be sown.

If the TER values are >1 (or the specific national level, if higher), then no further testing is necessary.

If the TER values are ≤1 (or the specific national level, if higher), damage to the relevant succeeding crops is possible and further field-testing is necessary as described under point 3 in EPPO PP 1/207.

It is necessary to consider when succeeding crops are likely to be sown in normal rotation but also when replacement crops may be sown in case of crop failure. If the TER values indicate there is a risk to the succeeding/replacement crops at the time when they could be sown, then field testing or restrictions on the possible succeeding crops are necessary.

Before determining if field testing or restrictions are necessary it is also possible to consider the effects of different cultivation methods. For example, ploughing to a depth of 15 cm would distribute the active substance(s) within a greater quantity of soil and as a result, the PEC_{soil} will be 1/3 of the amount compared to if minimal cultivation to a depth of 5 cm was used. As the PEC_{soil} will be lower, the TER will reach a value >1 at an earlier interval after application.

It is important to remember that the calculation of TER values is only the first step in a succeeding crops risk assessment and field trials may be necessary to demonstrate safety to rotational and replacement crops.

Method 1 – Formulated product risk assessment

The EC_{10} values in mg ∑ a.s./kg soil are compared with the PEC_{actual} values in mg ∑ a.s./kg soil. Therefore, only one set of TER values is calculated.

It is considered safe to sow a succeeding crop at the interval after application when the TER value is above the trigger value.

By using the combined EC_{10} value for all of the active substances in the product and the longest DT_{50} value, this method represents a worst-case risk assessment. This method takes into account the fact that each active substance will have a different inherent toxicity, but also that when multiple active substances are present in the soil simultaneously, they may have a cumulative or even synergistic effect.

An example of a succeeding crops risk assessment using this method can be found in Appendix 1.

Method 2 – Individual active substance(s) risk assessment

The EC_{10} values in mg a.s./kg soil for each active substance are compared with the PEC_{actual} values in mg a.s./kg soil for each active substance. A set of TER values are calculated for each individual active substance.

It may be safe to sow a succeeding crop at the interval after application when the TER values for all of the active substances within the product formulation are above the trigger value. However, it is important to note that this method does not take into account any potential cumulative or synergistic effects from having multiple active substances present in the soil simultaneously. These TER values should therefore be used with caution and expert knowledge will be required to determine appropriate sowing intervals. A combined risk assessment to take into account mixture toxicity may be used, if necessary.

If there is any uncertainty, then field testing or conservative succeeding crops restrictions will be necessary.

An example of a succeeding crops risk assessment using this method can be found in Appendix 2.

References

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directive 79/117/EEC and 91/414/EEC. Official Journal of the European Union L 309, 1-50.

Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:093:0085:0152:EN:PDF

OECD Guidance Documents for Pesticide Registration
http://www.oecd.org/env/ehs/pesticides-biocides/oecdguidancedocumentsforpesticideregistration.htm

Appendix 1

Example assessment of the impact on succeeding crops from a product formulation

Product X is a pre-emergence cereal herbicide containing 500 g/L of Active A and 100 g/L of Active B. The maximum dose is 1 L/ha.

The table below shows the results of a bioassay using 'Product X' at a range of concentrations incorporated in the soil. In this example, the EC_{10} values are expressed in terms of the total amount of active substance in the soil (i.e. mg Active A/kg soil + mg Active B/kg soil).

EC_{10} values produced in a bioassay where the product was incorporated in soil

Species	EC_{10} (mg ∑ a.s./kg soil)
Wheat	1.6
Barley	1.6
Oat	1.2
Ryegrass	0.76
Leek	0.72
Beans	0.60
Pea	0.60
Oilseed rape	0.48
Tomato	0.32
Sugar Beet	0.28
Carrot	0.24
Lettuce	0.20

As shown in the table above, the worst case EC_{10} value is 0.2 mg ∑ a.s./kg for lettuce.

The maximum dose of 1 L Product X/ha will deliver 500 g a.s./ha of Active A and 100 g a.s./ha of Active B, equivalent to a total of 600 g ∑ a.s./ha. Based on this total amount and a soil incorporation depth of 5 cm, the $PEC_{initial}$ value will be 0.8 mg ∑ a.s./kg

The DT_{50} values for Active A and Active B are 50 and 75 days respectively. The highest DT_{50} value of 75 days can be used as a worst-case when calculating the PEC_{actual} values in terms of mg ∑ a.s./kg soil. Therefore, the following PEC_{actual} values have been calculated:

PEC_{soil} values

Days after application	∑ active substance (mg ∑ a.s./kg soil)
0 (initial)	0.80
10	0.73
20	0.67
50	0.50
100	0.32
150	0.20
200	0.13

Using the PEC_{soil} values in the table above, along with the EC_{10} value in mg ∑ a.s./kg soil, TER values can be calculated (where TER = EC_{10} /PEC_{soil}). These are shown in the following table:

TER values

Days after application	TER
0	0.25
10	0.27
20	0.30
50	0.40
100	0.63
150	1.0
200	1.6

Assuming a trigger value of 1 to represent safety to the crop, the amount of active substance in the soil should be safe to lettuce (the most sensitive plant) 150 days after application.

Therefore, in this situation, it should be safe to sow all of the crops tested in the bioassay 150 days after an application of Product X. It will be necessary to consider at what point succeeding crops will be sown in normal rotation to determine if there is a risk. If it is possible for any succeeding crops to be sown <150 days after application of Product X, then there is a risk and further consideration is necessary. TER values should be calculated for the other succeeding crops at their relevant sowing dates. The effects of different cultivation methods could also be assessed at this point. For each species where a risk is identified, either field testing or restrictions on the possible succeeding crops are required.

In addition to the risk to succeeding crops sown in normal rotation, it is necessary to calculate the risk to replacement crops sown after crop failure. The initial PEC_{soil} can be used in this risk assessment as a TER > 1 indicates that there is no risk to replacement crops sown immediately after application. Alternatively, a relevant interval between application and sowing of replacement crops can be chosen and evaluated.

An example of a replacement crop risk assessment is shown in the table below, using Product X, an interval of 20 days after application and a soil incorporation depth of 5 cm, where the PEC_{soil} value is 0.67 mg ∑ a.s./kg:

Risk to replacement crops 20 days after application of Product X

Crop	EC_{10} (mg ∑ a.s./kg soil)	TER (at 20 DAA)
Lettuce	0.20	0.30
Carrot	0.24	0.36
Sugar beet	0.28	0.42
Tomato	0.32	0.48
Oilseed rape	0.48	0.72
Pea/beans	0.60	0.90
Leek	0.72	1.1

This risk assessment indicates that it should be safe to sow wheat, barley, oat, ryegrass and leek as replacement crops 20 days after application of Product X. There is a risk to the other crops, which will either need a longer interval or may not be appropriate replacement crops. The effects of different cultivation methods could also be assessed at this point. For each species where a risk is identified, either field testing or restrictions on the possible replacement crops are required.

Appendix 2

Example assessment of the impact on succeeding crops from the individual active substances within a product formulation

Product Y is a pre-emergence cereal herbicide containing 750 g/l of Active C and 50 g/l of Active D. The maximum dose is 1 L/ha.

The following table shows the results of separate bioassays where the active substances within 'Product Y' were applied individually at a range of concentrations incorporated in soil:

EC_{10} values produced in separate bioassays where the active substances were individually incorporated in soil

Species	Active C EC_{10} (mg/kg soil)	Active D EC_{10} (mg/kg soil)
Wheat	1.4	0.079
Barley	1.5	0.078
Oat	1.0	0.071
Ryegrass	0.65	0.064
Leek	0.61	0.058
Beans	0.51	0.034
Pea	0.51	0.033
Oilseed rape	0.41	0.021
Tomato	0.27	0.014
Sugar Beet	0.24	0.011
Carrot	0.20	0.0099
Lettuce	0.17	0.0084

The worst case EC_{10} values were for lettuce and were 0.17 mg/kg Active C and 0.084 mg/kg Active D.

The maximum dose of 1 L Product Y/ha will deliver 750 g a.s./ha of Active C and 50 g a.s./ha of Active D. Based on these application rates and a soil incorporation depth of 5 cm, the $PEC_{initial}$ will be 1.0 mg/kg for Active C and 0.067 mg/kg of Active D.

The DT_{50} values for Active C and Active D are 25 and 100 days respectively. Therefore, the following PEC_{actual} values have been calculated:

PEC_{soil} values

Days after application	Active C (mg/kg soil)	Active D (mg/kg soil)
0 (initial)	1.0	0.067
10	0.76	0.062
20	0.57	0.058
50	0.25	0.047
100	0.063	0.033
150	0.016	0.024
200	0.0039	0.017
300	0.00024	0.0083

Using the PEC_{soil} values in the table above, along with the worst case EC_{10} values for each active substance, TER values for lettuce as possible succeeding crop can be calculated (where TER = EC_{10} /PEC_{soil}). These are shown in the following table:

TER values

Days after application	Active C	Active D
0	0.17	0.13
10	0.22	0.14
20	0.30	0.14
50	0.68	0.18
100	2.7	0.25
150	10	0.36
200	44	0.50
300	696	1.0

Assuming a trigger value of 1 to represent safety to the crop, the amount of Active C in the soil should be safe to lettuce (the most sensitive plant) 64 days after application. The amount of Active D in the soil should be safe to lettuce 300 days after application.

Therefore, in this situation, it should be safe to sow all of the following crops tested in the bioassay 300 days after an application of Product Y. The amount of Active C remaining in the soil after 300 days is unlikely to have a negative effect on succeeding crops.

It will be necessary to consider at what point succeeding crops will be sown in normal rotation to determine if there is a risk. If it is possible for any succeeding crops to be sown <300 days after application of Product Y, then there is a risk and further consideration is necessary. TER values should be calculated for the other succeeding crops at their relevant sowing dates. The effects of different cultivation methods could also be assessed at this point. For each species where a risk is identified, either field testing or restrictions on the possible succeeding crops are required.

In addition to the risk to succeeding crops sown in normal rotation, it is necessary to calculate the risk to replacement crops sown after crop failure. The initial PEC_{soil} can be used in this risk assessment as a TER > 1 indicates that there is no risk to replacement crops sown immediately after application. Alternatively, a relevant interval between application and sowing of replacement crops can be chosen and evaluated.

An example of a replacement crop risk assessment is shown in the table below, using Product Y, an interval of 20 days after application and a soil incorporation depth of 5 cm, where the PEC_{soil} values are 0.57 mg/kg soil and 0.058 mg/kg soil for Active C and D respectively:

Risk to replacement crops 20 days after application of Product Y

Crop	EC_{10} (mg/kg soil)		TER (at 20 DAA)	
	Active C	Active D	Active C	Active D
Wheat	1.4	0.079	2.5	1.4
Barley	1.5	0.078	2.6	1.3
Oat	1	0.071	1.8	1.2
Ryegrass	0.65	0.064	1.1	1.1

Leek	0.61	0.058	1.1	1.0
Beans	0.51	0.034	0.9	0.6
Pea	0.51	0.033	0.9	0.6
Oilseed rape	0.41	0.021	0.7	0.4
Tomato	0.27	0.014	0.5	0.2
Sugar Beet	0.24	0.011	0.4	0.2
Carrot	0.2	0.0099	0.4	0.2
Lettuce	0.17	0.0084	0.3	0.1

This risk assessment indicates that it may be safe to sow wheat, barley, oat, ryegrass and leek as replacement crops 20 days after application of Product Y. However, as both active substances will be present in the soil simultaneously, it may be best to cultivate/plough before sowing these replacement crops. There is a risk to the other crops, which will either need a longer interval or may not be appropriate replacement crops. The effects of different cultivation methods could also be assessed at this point. For each species where a risk is identified, either field testing or restrictions on the possible replacement crops are required.

Appendix 3

Conversion of ER_{10}/ED_{10} values into EC_{10} values

EC_{10} values in mg a.s./kg soil are the basis for the calculation of TER values, as they are in the same units as the PEC_{soil} values.

In a typical succeeding crop bioassay, the product/active substance is incorporated into the pots at a range of concentrations in mg a.s./kg soil. The concentrations tested can be used to calculate the EC_{10} values.

However, in some bioassays, the product/active substance may be applied to the pots at a range of doses per unit area, prior to their incorporation within the soil. In these bioassays, the endpoints will be ER_{10}/ED_{10} values rather than EC_{10} values and will be expressed as an amount of product/active substance per unit area (for example g a.s./ha).

These ER_{10}/ED_{10} values must be converted into EC_{10} values. This conversion can be done using an equation equivalent to the $PEC_{initial}$ calculation, as follows:

$$EC10 = \frac{ER10}{100\ x\ soil\ depth\ x\ soil\ density}$$

Units:

EC_{10}	= mg ∑ a.s./kg soil
ER_{10}	= g ∑ a.s./ha
Soil depth	= cm
Bulk soil density	= g/cm^3

The values used in this calculation must be explained and justified. It may be appropriate to use the actual soil depth and density in the pots used in the bioassay.