COMMISSION DIRECTIVE 96/68/EC

of 21 October 1996

amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market (1), as last amended by Commission Directive 96/46/EC (2), and in particular Article 18 (2) thereof,

Whereas Annexes II and III to Directive 91/414/EEC set out the requirements for the dossier to be submitted by applicants respectively for the inclusion of an active substance in Annex I and for the authorization of a plant protection product;

Whereas it is necessary to indicate, to the applicants, in Annexes II and III, as precisely as possible, any details on the required information, such as the circumstances, conditions and technical protocols under which certain data have to be generated; whereas these provisions should be introduced as soon as available in order to permit applicants to use them in the preparation of their files;

Whereas it is now possible to introduce more precision with regard to the data requirements concerning residues in or on treated products, food and feed of the active substance provided for in Section 6 of Part A of Annex II;

Whereas it is also now possible to introduce more precision with regard to the data requirements concerning residues in or on treated products, food and feed of the plant protection product provided for in Section 8 of Part A of Annex III;

Whereas the measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Plant Health,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 91/414/EEC is amended as follows:

1. In Part A of Annex II the Section headed '6. Residues in or on treated products, food and feed' is replaced by Annex I hereto.

2. In Part A of Annex III in Section 7, under the heading '7.2. Data on exposure' the following text is inserted:

   'When measuring exposure to a plant protection product in the air within the breathing area of operators, bystanders or workers the requirements for measuring procedures described in Annex II A to Council Directive 80/1107/EEC of 27 November 1980 on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work (*) have to be taken into account.

   (*) OJ No L 327, 3. 12. 1980, p. 8.'

3. In Part A of Annex III the Section headed '8. Residues in or on treated products, food and feed' is replaced by Annex II hereto.

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 30 November 1997. They shall immediately inform the Commission thereof.

When Member States adopt these measures, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 3

This Directive shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Communities.*

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 21 October 1996.

For the Commission

Franz FISCHLER

Member of the Commission

(1) OJ No L 230, 19. 8. 1991, p. 1.
(2) OJ No L 214, 23. 8. 1996, p. 18.

ANNEX I

Section 6 of Part A of Annex II to Directive 91/414/EEC is replaced by the following:

'6. RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Introduction

(i) The information provided, taken together with that provided for one or more preparations containing the active substance, must be sufficient to permit an evaluation to be made as to the risks for man, arising from residues of the active substance and relevant metabolites, degradation and reaction products remaining in food. In addition, the information provided must be sufficient to:

— permit a decision to be made as to whether, or not, the active substance can be included in Annex I,

— specify appropriate conditions or restrictions to be associated with any inclusion in Annex I.

(ii) A detailed description (specification) of the material used, as provided under Section 1, point 11 must be provided.

(iii) Studies should be performed according to the guidance available on regulatory testing procedures for residues of plant protection products in food (*).

(iv) Where relevant, data should be analyzed using appropriate statistical methods. Full details of the statistical analysis should be reported.

(v) Stability of residues during storage.

If may be necessary to perform studies on the stability of residues during storage. Provided samples are frozen within generally 24 hours after sampling and unless a compound is otherwise known to be volatile or labile, data are not normally required for samples extracted and analysed within 30 days from sampling (six months in the case of radio-labelled material).

Studies with non-radio-labelled substances should be carried out with representative substratets and preferably on samples from treated crops or animals with incurred residues. Alternatively, if this is not possible, aliquots of prepared control samples should be spiked with a known amount of chemical before storage under normal storage conditions.

Where the degradation during storage is significant (more than 30 %) it may be necessary to change the storage conditions or not to store the samples prior to analysis and repeat and studies where the unsatisfactory storage conditions were used.

Detailed information with respect to the sample preparation and storage conditions (temperature and duration) of samples and extracts must be submitted. Storage stability data using sample extracts will also be required unless samples are analysed within 24 hours of extraction.

6.1. **Metabolism, distribution and expression of residue in plants**

Aim of the tests

The objectives of these studies are:

— to provide an estimate of total terminal residues in the relevant portion of crops at harvest following treatment as proposed,

— to identify the major components of the total terminal residue,

— to indicate the distribution of residues between relevant crops parts,

— to quantify the major components of the residue and to establish the efficiency of extraction procedures for these components,

— to decide on the definition and expression of a residue.

Circumstances in which required

These studies must always be performed unless it can be justified that no residues will remain on plants/plant products which are used as food or feedingstuffs.

(*) Guidance under development.

Test conditions

Metabolism studies have to involve crops or categories of crops in which plant protection products containing the active substance in question would be used. If a wide range of uses in different crop categories or in the category fruits is envisaged, studies have to be carried out on at least three crops unless it can be justified that a different metabolism is unlikely to occur. In cases where use is envisaged in different categories of crops, the studies must be representative for the relevant categories. For this purpose crops can be considered as falling into one of five categories: root vegetables, leafy crops, fruits, pulses and oilseeds, cereals. If studies are available for crops from three of these categories and the results indicate that the route of degradation is similar in all three categories then it is unlikely that any more studies will be needed unless it could be expected that a different metabolism will occur. The metabolism studies have also to take into account the different properties of the active substance and the intended method of application.

An evaluation of the results from different studies has to be submitted on the point and path of uptake (e.g. via leaves or roots), and on the distribution of residues between relevant parts of the crop at harvest (with particular emphasis on edible parts for man or animals). If the active substance or relevant metabolites are not taken up by the crop, this must be explained. Information on the mode of action and the physico-chemical properties of the active substance may be helpful in assessing trial data.

6.2. **Metabolism, distribution and expression of residue in livestock**

Aim of tests

The objectives of these studies are:

— to identify the major components of the total terminal residue in edible animal products,

— to quantify the rate of degradation and excretion of the total residue in certain animal products (milk or eggs) and excreta,

— to indicate the distribution of residues between relevant edible animal products,

— to quantify the major components of the residue and to show the efficiency of extraction procedures for these components,

— to generate data from which a decision on the need for livestock feeding studies as provided for in point 6.4 can be made,

— to decide on the definition and expression of a residue.

Circumstances in which required

Metabolism studies on animals, such as lactating ruminants (e.g. goat or cow) or laying poultry, are only required when pesticide use may lead to significant residues in livestock feed ($\geq$ 0,1 mg/kg of the total diet as received, except special cases e.g. active substances which accumulate). Where it becomes apparent that metabolic pathways differ significantly in the rat as compared to ruminants a pig study must be conducted unless the expected intake by pigs is not significant.

6.3. **Residue trials**

Aim of the tests

The objectives of these studies are:

— to quantify the highest likely residue levels in treated crops at harvest or outloading from store following the propopsed good agricultural practice (GAP),

and

— to determine, when appropriate, the rate of decline of plant protection product deposits.

Circumstances in which required

These studies must always be performed where the plant protection product will be applied to plants/plant products which are used as food or feedingstuffs or where residues from soil or other substrates can be taken up by such plants except where extrapolation from adequate data on another crop is possible.

Residue trial data shall be submitted in the Annex II dossier for those uses of plant protection products for which authorization is sought at the moment of introduction of a dossier for inclusion of the active substance in Annex I.

Test conditions

Supervised trials should corrspond to proposed critical GAP. The test conditions must take into account the highest residues which may reasonably arise (e.g. maximum number of proposed applications, use of the maximum envisaged quantity, shortest pre-harvest intervals, withholding periods or storage periods) but which remain representative of the realistic worst case conditions in which the active substance would be used.

Sufficient data must be generated and submitted to confirm that patterns determined hold for the regions and the range of conditions, likely to be encountered in the regions concerned for which its use is to be recommended.

When establishing a supervised trial programme, normally factors such as climatic differences existing between production areas, differences in production methods (e.g. outdoor versus glasshouse uses), seasons of production, type of formulations, etc. should be taken into account.

In general, for a comparable set of conditions, trials should be carried out over a minimum of two growing seasons. All exceptions should be fully justified.

The precise number of trials necessary is difficult to determine in advance of a preliminary evaluation of the trial results. Minimum data requirements only apply where comparability can be established between production areas, e.g. concerning climate, methods and growing seasons of production, etc. Assuming all other variables (climate, etc.) are comparable, a minimum of eight trials representative of the proposed growing area is required for major crops. For minor crops normally four trials representative of the proposed growing area are required.

Due to the inherently higher level of homogeneity in residues arising from post-harvest treatments or protected crops, trials from one growing season will be acceptable. For post-harvest treatments, in principle a minimum of four trials are required, carried out preferably at different locations with different cultivars. A set of trials has to be carried out for each application method and store type unless the worst case residue situation can be clearly identified.

The number of studies per growing season to be performed can be reduced if it can be justified that the residue levels in plants/plant products will be lower than the limit of determination.

Where a significant part of the consumable crop is present at the time of application, half of the supervised residue trials reported should include data to show the effect of time on the level of residue present (residue decline studies) unless it can be justified that the consumable crop is not affected by the application of the plant protection product under the proposed conditions of use.

6.4. Livestock feeding studies

Aim of the tests

The objective of these studies is to determine the residue in products of animal origin which will result from residues in feedingstuffs or fodder crops.

Circumstances in which required

Feeding studies are only required:

— when significant residues ($\geq$ 0,1 mg/kg of the total diet as received, except special cases, such as active substances which accumulate) occur in crops or part of the crop (e.g. trimmings, waste) fed to animals, and

— when metabolism studies indicate that significant residues (0,01 mg/kg or above the limit of determination if this would be higher than 0,01 mg/kg) may occur in any edible animal tissue taking into account the residue levels in potential feedingstuffs obtained at the 1 × dose rate.

Where appropriate separate feeding studies for lactating ruminant and/or laying poultry should be submitted. Where it appears from the metabolism studies submitted in accordance with the provisions of point 6.2 that metabolic pathways differ significantly in the pig as compared to ruminants, a pig feeding study must be conducted unless the expected intake by pigs is not significant.

Test conditions

In general, the feed is administered in three dosages (expected residue level, three to five times, and 10 times the expected residue level). When setting the 1 × dose, a theoretical feed ration must be compiled.

6.5. Effects of industrial processing and/or household preparations

Circumstances in which required

The decision as to whether it is necessary to carry out processing studies will depend on:

— the importance of a processed product in the human or animal diet,

— the level of residue in the plant or plant product to be processed,

— the physico-chemical properties of the active substance or relevant metabolites, and

— the possibility that degradation products of toxicological significance may be found after processing of the plant or plant product.

Processing studies are not normally necessary if no significant or no analytically determinable residues occur in the plant or plant product which would be processed, or if the total theoretical maximum daily intake (TMDI) is less than 10 % of the ADI. In addition, processing studies are not normally required for plants or plant products mostly eaten raw except for those with inedible portions such as citrus, banana or kiwi fruit where data on the distribution of the residue in peel/pulp may be required.

"Significant residues" generally refer to residues above 0,1 mg/kg. If the pesticide concerned has a high acute toxicity and/or a low ADI, consideration must be given to conducting processing studies for determinable residues below 0,1 mg/kg.

Studies on the effects on the nature of the residue are not normally required where only simple physical operations, not involving a change in temperature of the plant or the plant product, are involved such as washing, trimming or pressing.

6.5.1. Effects on the nature of the residue

Aim of the tests

The objective of these studies is to establish whether or not breakdown or reaction products arise from residues in the raw products during processing which may require a separate risk assessment.

Test conditions

Depending upon the level and chemical nature of the residue in the raw commodity, a set of representative hydrolysis situations (simulating the relevant processing operations) should be investigated, where appropriate. The effects of process other than hydrolysis, may also have to be investigated, where the properties of the active substance or metabolites indicate that toxicologically significant degradation products may occur as a result of these processes. The studies are normally conducted with a radio-labelled form of the active substance.

6.5.2. **Effects on the residue levels**

Aim of the tests

The main objectives of these studies are:

— to determine the quantitative distribution of residues in the various intermediate and end products, and to estimate transfer factors,

— to enable a more realistic estimate to be made of dietary intake of residues.

Test conditions

Processing studies should represent household processing and/or actual industrial processes.

In the first instance it is usually only necessary to carry out a core set of "balance studies" representative of the common processes relevant to the plants or plant products containing significant residues. Justification should be given for the selection made of these representative process(es). The technology to be used in processing studies should always correspond as closely as possible to the actual conditions that are normally used in practice. A balance sheet should be made in which the mass balance of residues in all intermediate and end products is investigated. In drawing up such a balance sheet any concentrations or reductions in residues in individual products can be recognized and the corresponding transfer factors can also be determined.

If the processed plant products play an important part in the diet, and if the "balance study" indicates that a significant transfer of residue into the processed products could occur, then three "follow-up studies" to determine residue concentration or dilution factors must be carried out.

6.6. **Residues in succeeding crops**

Aim of the test

The objective of these studies is to permit an evaluation of possible residues in succeeding crops.

Circumstances in which required

Where data generated in accordance with Annex II, Section 7, point 7.1 or Annex III, Section 9, point 9.1, shows that significant residues (> 10 % of the applied active substance as a total of unchanged active substance and its relevant metabolites or degradation products) remain in soil or in plant materials, such as straw or organic material up to sowing or planting time of possible succeeding crops, and which could lead to residues above the limit of determination in succeeding crops at harvest, consideration should be given to the residue situation. This should include consideration of the nature of the residue in the succeeding crops and involve at least a theoretical estimation of the level of these residues. If the likelihood of residues in succeeding crops can not be excluded, metabolism and distribution studies should be carried out, if necessary followed by field trials.

Test conditions

If a theoretical estimation of residues in succeeding crops is done, full details and a justification shall be be given.

Metabolism and distribution studies and field trials, if necessary, shall be carried out on representative crops chosen to represent normal agricultural practice.

6.7. **Proposed maximum residue levels (MRLs) and residue definiton**

A full justification for the propsoed MRLs must be provided, including, where relevant, full details of the statistical analysis used.

When judging which compounds are to be included in the residue definition, account has to be taken of the toxicological significance of the compounds, amounts likely to be present and the practicality of the analytical methods proposed for post-registration control and monitoring purposes.

6.8. **Proposed pre-harvest intervals for envisaged uses, or withholding periods or storage periods, in the case of post-harvest uses**

A full justification for the proposals must be provided.

6.9. **Estimation of the potential and actual exposure through diet and other means**

Consideration will be given to the calculation of a realistic prediction of dietary intake. This may be done in a step-wise fashion leading to an increasingly realistic predictions of intake. Where relevant, other sources of exposure such as residues arising from the use of medicines or veterinary drugs have to be taken into acocunt.

6.10. **Summary and evaluation of residue behaviour**

A summary and evaluation of all data presented in this Section should be carried out according to the guidance given by the competent authorities of the Member States concerning the format of such summaries and evaluations. It should include a detailed and critical assessment of those data in the context of relevant evaluative and decision-making criteria and guidelines, with particular reference to the risks for man and animals that may or do arise, and the extent, quality and reliablity of the data base.

In particular, the toxicological significance of any non-mammalian metabolites must be addressed.

A schematic diagram should be prepared of the metabolic pathway in plants and animals with a brief explanation of the distribution and chemical changes involved.'

ANNEX II

Section 8 of Part A of Annex III to Directive 91/414/EEC is replaced by the following:

'8. RESIDUES IN OR ON TREATED PRODUCTS, FOOD AND FEED

Introduction

The provisions of Annex II, Section 6, Introduction apply.

8.1. **Metabolism, distribution and expression of residue in plants or livestock**

Aim of the tests

The objectives of these studies are:

— to provide an estimate of total terminal residues in the relevant portion of crops at harvest following treatment as proposed,

— to quantify the rate of degradation and excretion of the total residue in certain animal products (milk or eggs) and excreta,

— to identify the major components of the total terminal residue in crops and in edible animal products respectively,

— to indicate the distribution of residues between relevant crop parts and between relevant edible animal products respectively,

— to quantify the major components of the residue and to show the efficiency of extraction procedures for these components,

— to generate data from which a decision on the need for livestock feeding studies as provided for in point 8.3 can be made,

— to decide on the definition and expression of a residue.

Circumstances in which required

Supplementary metabolism studies only need to be performed where it is not possible to extrapolate from data obtained on the active substance in accordance to the requirements of Annex II, Section 6, points 6.1 and 6.2. This might be the case for crops or for livestock for which data were not submitted in the framework of inclusion of the active substance in Annex I or were not necessary for amending the conditions of its inclusion in Annex I or where it could be expected that a different metabolism will occur.

Test conditions

The same provisions as provided under the corresponding paragraphs of Annex II, Section 6, points 6.1 and 6.2 apply.

8.2. **Residue trials**

Aim of the tests

The objectives of these studies are:

— to quantify the highest likely residue levels in treated crops at harvest or outloading from store following the proposed good agricultural practice (GAP),

and

— to determine, when appropriate, the rate of decline of pesticide deposits.

Circumstances in which required

Supplementary residue trials only need to be performed where it is not possible to extrapolate from data obtained on the active substance in accordance to the requirements of Annex II, Section 6, point 6.3. This might be the case for special formulations, for special application methods or for crops for which data were not submitted in the framework of inclusion of the active substance in Annex I or were not necessary for amending the conditions of its inclusion in Annex I.

Test conditions

The same provisions as provided under the corresponding paragraphs of Annex II, Section 6, point 6.3 apply.

8.3. **Livestock feeding studies**

Aim of the tests

The objective of these studies is to determine the residue in products of animal origin which will result from residues in feedingstuffs or fodder crops.

Circumstances in which required

Supplementary feeding studies for the purpose of assessing maximum residue levels for products of animal origin are only required where it is not possible to extrapolate from data obtained on the active substance in accordance to the requirements of Annex II, Section 6, point 6.4. This might be the case where additional fodder crops are to be authorized which leads to an increased intake of residues of livestock for which data were not submitted in the framework of inclusion of the active substance in Annex I or were not necessary for amending the conditions of its inclusion in Annex I.

Test conditions

The same provisions as provided under the corresponding paragraphs of Annex II, Section 6, point 6.4 apply.

8.4. **Effects of industrial processing and/or household preparations**

Aim of the tests

The main objectives of these studies are:

— to establish whether or not breakdown or reaction products arise from residues in the raw products during processing which may require a separate risk assessment,

— to determine the quantitative distribution of residues in the various intermediate and end products, and to estimate transfer factors,

— to enable a more realistic estimate to be made of dietary intake of residues.

Circumstances in which required

Supplementary studies only need to be performed where it is not possible to extrapolate from data obtained on the active substance in accordance to the requirements of Annex II, Section 6, point 6.5. This might be the case for crops for which data were not submitted in the framework of inclusion of the active substance in Annex I or were not necessary for amending the conditions of its inclusion in Annex I.

Test conditions

The same provisions as provided under the corresponding paragraphs of Annex II, Section 6, point 6.5 apply.

8.5. **Residues in succeeding crops**

Aim of the test

The objective of these studies is to permit an evaluation of possible residues in succeeding crops.

Circumstances in which required

Supplementary studies are only required where it is not possible to extrapolate from data obtained on the active substance in accordance to the requirements of Annex II, Section 6, point 6.6. This might be the case for special formulations, for special application methods or for crops for which data were not submitted in the framework of inclusion of the active substance in Annex I or were not necessary for amending the conditions of its inclusion in Annex I.

Test conditions

The same provisions as provided under the corresponding paragraphs of Annex II, Section 6, point 6.6 apply.

8.6. **Proposed maximum residue levels (MRLs) and residue definition**

A full justification for the proposed MRLs must be provided, including, where relevant, full details of the statistical analysis used.

If the metabolism studies submitted in accordance with the provisions of point 8.1 indicate that the residue definition should be changed taking into account the actual residue definition and the necessary judgement as outlined under the corresponding paragraph of Annex II, Section 6, point 6.7, a re-evaluation of the active substance may be necessary.

8.7. **Proposed pre-harvest intervals for envisaged uses, or withholding periods or storage periods, in the case of post-harvest uses.**

A full justification for the proposals must be provided.

8.8. **Estimation of the potential and actual exposure through diet and other means**

Consideration will be given to the calculation of a realistic prediction of dietary intake. This may be done in a step-wise fashion leading to an increasingly realistic prediction of intake. Where relevant, other sources of exposure such as residues arising from the use of medicines or veterinary drugs have to be taken into account.

8.9. **Summary and evaluation of residue behaviour**

A summary and evaluation of all data presented in this Section should be carried out according to the guidance given by the competent authorities of the Member States concerning the format of such summaries and evaluations. It should include a detailed and critical assessment of those data in the context of relevant evaluative and decision-making criteria and guidelines, with particular reference to the risks for man and animals that may or do arise, and the extent, quality and reliability of the data base.

Where metabolism data have been submitted the toxicological significance of any non-mammalian metabolites must be addressed.

A schematic diagram should be prepared of the metabolic pathway in plants and animals with a brief explanation of the distribution and chemical changes involved if metabolism data have been submitted.'