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(AS REVISED IN 2009)

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The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 30 industrialised countries in North America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in ten different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides and Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and the Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (http://www.oecd.org/ehs/).

This publication was produced within the framework of the Inter-Organisation Programme for the Sound Management of Chemicals (IOMC).

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The participating organisations are FAO, ILO, OECD, UNEP, UNIDO, UNITAR and WHO. The World Bank and UNDP are observers. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

FOREWORD

In 2003, the OECD initiated work to develop harmonised Test Guidelines and Guidance Documents on pesticide residue chemistry. Harmonised guidelines are essential to further work sharing goals of the Working Group on Pesticides for pesticide registration and re-registration. The harmonisation is based on guidelines currently used in Australia, Canada, Japan, the United States, the European Union and the Food and Agriculture Organisation (FAO) to provide for determination of pesticide exposure in food or animal feedstuffs. Data derived from such guidelines will not only be used by industry to fulfil pesticide registration requirements in countries/regions, but could also support FAO's development of recommendations on Maximum Residue Limits (MRLs). Several guidance documents and test Guidelines (and templates for reporting test study summary data) have been developed within these activities:

Guidance Documents:

- *Definition of Residue (series on Testing and Assessment, No.63)*
- *Overview of Residue Chemistry Studies (series on Testing and Assessment, No. 64)*
- *Guidance Document on Pesticide Residue Analytical Methods (series on Testing and Assessment, No. 72)*
- *Guidance Document on Magnitude of Pesticide Residues in Processed Commodities (series on Testing and Assessment, No. 96)*

Test Guidelines:

- *TG 501:Metabolism in Crops,*
- *TG 502: Metabolism in Rotational Crops,*
- *TG 503: Metabolism in Livestock,*
- *TG 504: Residues in Rotational Crops (Limited Field Studies),*
- *TG 505: Residues in Livestock*
- *TG 506: Stability of Pesticide Residues in Stored Commodities*
- *TG 507: Nature of Pesticide Residues in Processed Commodities – High Temperature Hydrolysis*
- *TG 508: Magnitude of Pesticide Residues in Processed Commoditie*
- *TG 509: Crop Field Trial (To be publiched late 2009)*

The Test Guidelines and Guidance Documents were drafted by an OECD Expert Group on Pesticide Residue Chemistry, chaired by the United States and composed of experts from Australia, Canada, Germany, Italy, Japan, the Netherlands, New Zealand, the United Kingdom, the United States, the European Commission, the European Food Safety Authority (EFSA), FAO and CropLife International/ BIAC. A small Steering Committee organised the work and identified issues for the Expert Group; it is composed of roughly one Expert Group member per different region (North America, Europe, Asia and Oceania) and organisation (EC, FAO and OECD). The work was carried out by drafting groups drawn from the Expert Group, one for each guideline and guidance document. The Expert Group reported to the Registration Steering Group/Working Group on Pesticides (RSG/WGP), which had management oversight of the initial phase of development up to production of draft proposals; the draft documents were then submitted to the Working Group of National Co-ordinators of the Test Guidelines Program (WNT).

The harmonised Guidance for the Definition of Residue provides a common approach to residue identification of the pesticide and its metabolites and degradation products. Residue analysis for dietary risk assessment emphasizes analysis of the parent compound and its most significant metabolites and degradates, taking into consideration both exposure and relative toxicities.

For MRL enforcement, the residue definition may be comprised of a subset of the components included in the definition for dietary risk assessment. That subset would include 'marker compounds' or 'indicator molecules' which typically would account for a substantial proportion of the residue determined by a data gathering method.

Residue analysis for tolerance/MRL enforcement purposes focuses on those 'analytes' which would indicate a possible misuse of the pesticide and which can be quantified by a broad base of national laboratories The Guidance Document on the Definition of Residue balances these concerns so that the appropriate chemical moieties can be analyzed. It differentiates residue definitions for data generation and risk assessment purposes *versus* MRL/tolerance-setting and enforcement purposes. Such guidance will be available to pesticide applicants so that they may propose definitions of residue for each purpose and provide data for implementation.

This document is an update of document (ENV/JM/MONO(2006)31. It takes into account comments and experiences reported from users in OECD countries since then. It provides a more detailed explanation of the 'marker compound' concept. In addition examples have been added or updated to provide improved clarity for the Definition of the Residue selection.

This document is published on the responsibility of the Joint Meeting of the Chemicals Group and Management Committee of the Special Programme on the Control of Chemicals of the OECD.

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Introduction

1. A pesticide residue is the combination of the pesticide and its metabolites, degradates, and other transformation products on human foods, livestock feeds, and/or drinking water. The number of distinct chemical compounds in the residue may vary significantly from pesticide to pesticide. In some cases, only the parent pesticide may be found on treated commodities, while other pesticides produce dozens of metabolites. For each pesticide used on food or feed commodities, regulatory authorities need to choose which residue(s) will be used for (i) dietary risk assessment and (ii) setting and enforcing tolerances/Maximum Residue Limits (MRLs). The term "definition of residue" or "residue definition" is used to refer to those residues chosen for these two regulatory purposes.

2. Residue analysis for risk assessment emphasizes analysis of the parent compound and its toxicologically significant metabolites, taking into consideration both exposure and relative toxicities. Residue analysis for tolerance/MRL enforcement purposes focuses on those analytes which would indicate a possible misuse of the pesticide and which also can be detected and measured by a broad base of national laboratories (i.e., residues which are easy to measure (ideally by a multi-residue method), normally occur in large quantities, and are common to all commodities in which residues are expected). A monitoring method based on one analyte allows greater utility by compliance authorities and minimizes the need to obtain expensive reference compounds. The most important concept is to define the residue for enforcement purposes as a single compound as far as possible. In this guidance document the term ‘marker compound’ will be used to refer to that single compound.

3. The Definition of Residue guidance balances these concerns so that the appropriate chemical moieties can be analyzed. This guidance document provides a harmonized approach for the residue definition that can be used by applicants during the process of generating residue data and by regulatory authorities during the review of such data. It has been developed from elements of several national and international guidance documents (see Bibliography).

General Considerations

4. The meaning of the term "pesticide residue" as the combination of the pesticide, its metabolites, degradates, and other transformation products has been adapted in a slightly revised form from the Food and Agriculture Organization Manual (FAO 2002), which also provides an internationally harmonized approach to Maximum Residue Limit (MRL) setting. Such residues may arise in food and feed products from current Good Agricultural Practice (GAP; synonymous with the term authorized uses) or from environmental contamination due to former agricultural practices and other sources of pollution (e.g., manufacturing).

5. Residue definitions that are the result of compromise between competing requirements may sometimes appear arbitrary. The basic requirements for the definition of residues are that it should:

1. include compounds of toxicological interest for dietary intake estimations and risk assessment, and

2. be the most suitable for setting an MRL/tolerance.

6. The two requirements are sometimes not compatible and, as a compromise, various definitions of residues are possible. For some compounds it may be necessary to establish separate residue definitions for MRL setting and for risk assessment. The residue definition for risk assessment should include metabolites and degradates of toxicological concern irrespective of their source, whereas the residue definition for

MRLs needs to be simple (i.e., use of a marker compound where possible), and suitable for practical routine monitoring and enforcement of the MRL at a reasonable cost.

7. It should be stressed that in choosing the appropriate analytes and the analytical methods, for data gathering in pre-registration trials and for post-registration monitoring of residue samples, the needs of both risk assessment and MRL enforcement need to be considered. In practice this will mean generating the data in such a way as to give the flexibility to establish two separate residue definitions where appropriate. In cases, where a suitable marker compound is available for MRL enforcement, but it is likely that a multi-component residue definition will be needed for risk assessment purposes, samples from supervised field trials (also known as crop field trials) should be either:

1. analysed separately for the individual components of the residue defined for risk assessment, where analytical methods allow, rather than carrying out a total residue analysis, or

2. if total residue methodology or common moiety methodology is being used to produce data for risk assessment, and the suitable marker compound can be analysed with a multi residue procedure, a second series of analyses of the supervised field trial samples might be carried out for the marker compound only (e.g., parent compound).

8. This approach allows the risk assessment to be carried out on the toxicologically significant residue components while ensuring that data are available to allow a different simple residue definition to be established, where appropriate, for MRL enforcement.

9. The following factors may be considered when proposing a residue definition:

- The composition and levels of the residues found in plant metabolism studies and animal metabolism studies (including rats).

- The toxicological properties of metabolites, degradates, and other transformation products including considerations of the toxicological significance of those metabolites and products compared to the active ingredient.

- Magnitude of residues determined in supervised residue trials and feeding studies.

- The possibility of the presence of a metabolite, degradate, or other transformation product common to another pesticide.

- The possibility of the pesticide itself being a metabolite, degradate, or transformation product of another pesticide.

- The availability of specific analytical methods and the practicality of regulatory analytical methods.

- National and international residue definitions already established.

- Where feasible harmonize residue definitions already established for veterinary drugs with those from agricultural pesticides that may leave residues in livestock commodities

- The possibility of a residue also being present as a natural substance.

10. Transgenic and non-transgenic crops may metabolise the pesticide differently. The principles for deciding residue definition do not change and depend strongly on metabolism and analytical methods. When a commodity produced by a non-transgenic crop cannot be readily distinguished from the transgenic crop commodity, the residue definition should be the same for both. No single approach is applicable to all situations and a case-by-case approach is needed at present.

11. The metabolites, degradates, and other transformation products have generally been identified and quantified in metabolism experiments with methods based on the use of isotope labelled compounds. Typically, the following metabolism and environmental fate data are available (at a maximum):

For crops and animals

- plant metabolism
- metabolism in livestock animals
- metabolism in fishes (for certain aquatic uses)
- metabolism in rats
- nature of residues in processed products
- metabolism in rotational crops

For drinking water considerations

- soil metabolism (aerobic and anaerobic)
- aqueous and soil photolysis
- hydrolysis

12. In cases of residues relating to persistent active ingredients arising from former agricultural practice of no longer registered plant protection products, the above-mentioned data might not be available. Consequently, the residue definition is sometimes established on the basis of the currently available information, such as monitoring data. Frequently, the active ingredient will be used for residue definition in cases where little knowledge exists on the behaviour of this compound in plants or livestock animals.

Residue Definition for Dietary Risk Assessment

13. Metabolites, degradates, or other transformation products (hereafter collectively referred to as "metabolite/degradate") that significantly contribute to the dietary risk should be included in the exposure assessment. For each metabolite/degradate to be considered to contribute significantly to the risk, two factors must be addressed: 1) the **potential for exposure** to the metabolite/degradate in the human diet; and 2) the **relative toxicity** of the metabolite/degradate to the parent. Metabolites/degradates with higher potential exposures and toxicities are more likely to be included in the dietary assessment.

Potential for Exposure

14. Parent Compound: The parent compound is included in dietary risk assessments in the vast majority of cases. However, in those instances where no residues of the parent are observed under GAP for all anticipated uses of the pesticide in the respective supervised field trials, while quantifiable levels of metabolites/degradates are present, it may be appropriate to exclude the parent compound from the definition of residue for risk assessment.

15. Major Metabolites: For the purposes of discussion, major metabolites are considered to be those which at any point in time contribute to 10% or more of the total radioactive residue (TRR) in metabolism studies in plants, livestock, or rotational crops. Similarly, major environmental degradates are those which represent 10% or more of the applied dose in environmental fate studies at any point in time. The following factors are considered when determining the need to include major metabolites/degradates in risk assessments:

- *Higher exposure:* Major metabolites/degradates found in commodities which are human foods (as opposed to animal feeds) have higher exposure potential. In countries where impacts of residues on animal health are considered, however, major metabolites in animal feed might be included in the residue definition. In addition, major residues on animal feed which readily transfer to meat, milk, or eggs based on livestock metabolism or feeding studies also need to be considered for inclusion. Increased mobility in soil and/or environmental persistence relative to the parent are considered to increase the potential exposure to degradates in drinking water. Therefore, such metabolites/degradates are more likely to be included in the dietary risk assessment.

- *Lower exposure:* Major metabolites/degradates found in only one matrix at 10-20% of the total residue have less exposure potential than those which occur at higher levels or in more matrices. Residues which are major in terms of percentage of the TRR, but present at very low absolute levels (mg/kg) also have lower exposure potential. If a compound strongly binds to soil, the level in drinking water is expected to be reduced. If the degradate of a pesticide occurs in a relatively unimportant environmental compartment, the resulting drinking water concentrations may also be negligible (e.g., a degradate of a terrestrial use pesticide which only occurs as a result of aqueous photolysis and the parent has a low potential to reach surface water). It is also appropriate to consider the time point at which a degradate reaches its maximum concentration. For example, a degradate which exceeds 10% of the applied dose early in a fate study, but dissipates rapidly to much lower levels, may not be a significant residue in drinking water. Therefore, such a degradate is less likely to be included in the risk assessment. Similarly, in the case of residues on crops, a metabolite which exceeds 10% only shortly after application whilst only long preharvest intervals are anticipated, may not be a significant residue.

- *Abundance Only in Feed Item:* Although a metabolite may represent >10% of the TRR in a plant matrix, it is unlikely to be included in the risk assessment if found only in livestock feed items at low levels (expressed in mg/kg), unless a strong potential for bioconcentration in fat tissues has been observed.

- *Levels of metabolite/degradate in magnitude of residue or environmental fate studies:* Occasionally a metabolite/degradate may be found in metabolism or laboratory environmental fate studies, but not found, or found in very low levels, in magnitude of residue (e.g., supervised or crop field trials, livestock feeding), water monitoring or field dissipation studies. In such cases, it is less likely to be included in the dietary assessment. If, however, the metabolite/degradate is found in greater abundance in the magnitude of residue/water monitoring studies than was anticipated based on the nature of the residue/laboratory fate studies, then it is more likely to be included in the risk assessment.

16. Some of the metabolites/degradates recommended for inclusion in the risk assessment may not be easily quantified. In such cases, non-standard means may have to be used when considering them in the quantitative assessment. Such recommendations often involve using a ratio obtained from a metabolism study for the residue level of the metabolite/degradate to the parent or another metabolite/degradate that is quantified by available analytical methods.

17. Minor Metabolites. Metabolites or degradates that comprise less than 10% of the TRR (or applied dose in environmental studies) are classified as minor metabolites or degradates. Minor metabolites are typically not included in the dietary risk assessment, as they generally do not contribute significantly to the exposure. However, they may be considered in the situations outlined below.

- Minor metabolites are known, or suspected, to be considerably more toxic than the parent compound.
- The analytical method for data collection is a common moiety method and includes several metabolites, including minor ones.
- Very few or no major residues are observed and numerous minor metabolites of toxicological significance collectively comprise a substantial portion of the TRR.

18. Theoretical Metabolites: Metabolites/degradates which were not found in the nature of the residue and/or environmental fate studies, but are theoretically possible, may also be considered. Such considerations arise when the parent compound has a moiety that is of known toxicity, but was not identified in the metabolism studies. In cases of such a concern, additional studies might be needed. An example of this includes a pesticide with an aniline ring, but the aniline ring was not labelled in the metabolism study, so that identification of the free aniline would be very difficult.

Toxicity Considerations for Metabolites/Degradates

19. In order to assess a metabolite/degradate toxicity and determine its potential effects, available information on the metabolite/degradate or similar compounds in databases or publications is evaluated. (See Annex 1**).** In some cases, however, toxicity data specific to the metabolite/degradate in question are not available or are limited to acute oral median lethal dose tests. In these instances weight of evidence evaluations are used to assess the toxic potential of the metabolite/degradate relative to that of the parent compound. The goal is to predict whether the metabolite/degradate is likely to be significantly less toxic than the parent, have comparable toxicity, be potentially significantly more toxic than the parent, or possess a different mechanism of toxicity. In many instances, it will not be clear as to whether a metabolite/degradate has the same mechanism of toxicity and/or how the level of toxicity would compare to that of the parent. The default position in such cases would be that the metabolite/degradate elicits the same effect as the parent and at comparable doses (i.e., equal toxicity).

20. In the process of metabolism or degradation, the toxic moiety may be unaffected, modified, or totally removed from the molecule. Alternatively, a new toxic moiety may be created. The parent compound may also be metabolized such that it is more rapidly excreted from the body, or its absorption and distribution characteristics may be significantly modified. It may be possible to predict whether the metabolite/degradate has the same mechanism of toxicity as the parent (i.e., would contribute to the toxicological endpoint(s) chosen for dietary risk assessment for the parent). In this case, the magnitude of the toxicity of the metabolite/degradate relative to that of the parent pesticide may also be predicted. Some of the questions typically considered to define residue for risk assessment are:

1. How toxic is the parent compound and what are relevant endpoints? In some cases toxicity data are not available for the metabolites and they are assumed to possess the same toxicity as the parent. In these situations, the more toxic the parent compound (with regard to effects and dosage) the greater the need to ensure all relevant metabolites/degradates are included in the assessment. Conversely, if the parent compound is of low toxicity, then the inclusion of the metabolite/degradate may not be necessary.

2. Has the mechanism of toxicity for the parent compound been characterized? If so, it has to be determined if toxicity of the metabolite/degradate involves the same mechanism. If the metabolite/degradate does not have the same mechanism of toxicity as the parent compound, it should not be included in the risk assessment for the parent pesticide. In some cases a separate assessment for the metabolite/degradate based on a different toxicological effect may be needed..See paragraph 21 on Separate Assessments for Metabolites and Degradates.

3. Does the metabolite/degradate occur **in metabolism studies such as those commonly performed in the rat** in significant quantities? If this is not the case then then any toxic effect it may produce may not have been seen in the mammalian toxicity studies. Therefore, there may be a greater need to include the metabolite/ degradate in the exposure/risk assessment and additional toxicological data regarding this compound might be needed.

4. Does the metabolite/degradate share toxic moieties with compounds of known toxicity other than the parent pesticide? It may be possible to determine the toxic mechanism of the metabolite/degradate compared to the parent based on information obtained from reference databases on chemicals which are structurally similar (i.e., have the same toxic moiety) to the metabolite/degradate. However, if the compound in the reference database possesses additional toxic moieties *versus* the metabolite/degradate, its utility for toxicity predictions is greatly reduced or eliminated.

5. Is the metabolite/degradate more hydrophilic and likely to be more rapidly excreted than the parent? If so, the metabolite/degradate is less likely to be considered of toxicological concern barring the presence of a new toxic moiety.

6. If the metabolite/degradate is a conjugate, is it likely to release a more toxic compound in the mammalian digestive system? In general, if the free form of a metabolite/degradate is considered to be of toxicological concern, the conjugates (e.g., glucosides, glucuronides) are also of concern due to their potential to be converted back to a biologically active compound following hydrolysis in the mammalian digestive system.

7. Are any novel metabolites/degradates of toxicological concern formed during processing (e.g., formation of ethylene thiourea (ETU) during processing (heating) of plant products containing residues of ethylene bisdithiocarbamates (EBDCs))? If so, these metabolite/degradates may also have to be considered in the risk assessment.

Separate Assessments for Metabolites and Degradates

21. For some chemicals, limited toxicity data may be available for the metabolites and degradates of interest, but rarely will a full toxicity data set be available. These data occasionally indicate separate consideration in the risk assessment for the relevant metabolite/degradate. For example, the metabolite/degradate may show similar effects as the parent compound, but toxicity of the metabolite/degradate may occur at lower doses meaning that the metabolite/degradate is more toxic. In those cases where sufficient data and information are available, scaling with uncertainty factors or relative toxicity factors can be considered to normalize the toxicity data. In other cases, it may be determined that the metabolite/degradate is not likely to produce adverse effects which are similar to the parent, but may have some toxicity at relevant doses in a manner different than the parent compound. In such cases a separate assessment for the metabolite/degradate may be recommended.

Combining Exposure and Toxicity Considerations

22. Using a weight of evidence approach, the various factors for exposure potential and toxicity for parent and metabolites/degradates are considered to make a decision on the residue definition for risk assessment purposes. These decisions are often far from being straight forward as can be illustrated by the following example.

23. For some low application rate herbicides (e.g., sulfonylureas), it is not unusual to find a number of major (>10% TRR) metabolites present at very low levels (often around 0.01 ppm or less) along with comparable or even lower levels of the parent pesticide. None of the individual residues may be found above the limit of quantitation (LOQ) of a typical enforcement method. From a human toxicity perspective these herbicides are generally of low concern. Although the metabolites are also of low concern, it usually cannot be concluded they are significantly less toxic than the parent pesticide. Therefore, if one were to apply the criteria outlined in this document, it would not seem reasonable to declare the parent the sole residue to be included for risk assessment (or for MRL/tolerance setting). However, given the low mammalian toxicity of many of these chemicals, the limited potential for misuse (due to their phytotoxicity), and the fact that the LOQ of the enforcement method may be greater than the TRR observed in the plant metabolism studies, regulatory authorities as a practical matter often conclude that the parent by itself may serve as the definition of residue for risk assessment (and MRL/tolerance setting) purposes.

24. Tables 1and 2 provide some considerations or situations where major metabolites/degradates may be included in the residue definitions for enforcement and risk assessment. However, these tables are meant to provide guidance only and should not be used as a checklist, as each case will be different.

For example, metabolites more polar than the parent compound can occur in significant amounts and still might cause toxicity through the same mechanism as the parent compound, but their toxicological potency can be much less as compared to the parent compound. Therefore, these metabolites are less likely to be included into the definition of the residue (DoR). With any decision, the occurrence, relative concentrations and toxicological properties have to be taken into account to see whether the inclusion of metabolites to the DoR leads to an improved MRL enforcement or exposure assessment.

Residue Definition for MRL Setting/Tolerance Expression

25. Although metabolites, degradates, and other transformation products are included in the definition of pesticide residues for risk assessment purposes, this does not necessarily mean that these metabolites, degradates, or other transformation products should always be included in the MRL/tolerance residue definition. Inclusion of transformation products in the residue definition depends on a number of factors, and the decision on whether they should be included is complex and decisions have to be made on a case-by-case basis. The most important concept is to define the residue as a single compound (marker compound) as far as possible. An exception would be stereoisomers (compounds of the same general chemical structure but differing in geometrical configuration at a single location in the molecule), which requires the selection of more than one single marker compound unless evidence that allows exclusion of certain isomers is provided. Adherence to a single compound as a marker residue has several advantages for national authorities. A single analytical method is preferred for residue control purposes; it allows more monitoring and surveillance of residues in food, and, in general, it reduces the analytical uncertainties associated with residue analysis when compared to situations in which more than one analysis may be required to determine compliance with an MRL. For example for livestock commodities it may be appropriate for monitoring purposes to select a marker compound if it is present in all commodities in all

instances. As the metabolic pattern in crops and in livestock metabolism can differ, different marker compounds for livestock and crop commodities might be necessary. While it should be avoided if at all possible, in exceptional cases it may even be necessary to have different marker compounds for different crop types (e.g., root crops versus leafy vegetables). In many cases the active ingredient used forms a major part in the residue and will be taken to define the residue. The methods used for supervised trials may be complicated or require sophisticated, expensive instrumentation and therefore are difficult to implement for regulatory analytical work. Furthermore, some countries may experience extreme difficulty obtaining metabolites for use as standards in the analytical work. Therefore, inclusion of metabolites in the residue definition, particularly polar metabolites, is often not practical for monitoring/enforcement of MRLs/tolerances.

Table 1: Considerations for Major (>10% of the TRR) Metabolites/Degradates to be included in the Risk Assessment

More likely to be included	Less likely to be included
• Parent compound is highly toxic. • Metabolite/degradate likely to be found in commodities that are human foods. • Metabolite/degradate levels in magnitude of residue studies exceeded those expected from metabolism studies. • Metabolite/degradate likely to cause toxicity through the same mechanism of action as the parent compound. • Metabolite/degradate is not formed through metabolism in rats. • Parent compound was non-detectable, but metabolites were found in high levels in metabolism studies. **Considerations for drinking water:** • Environmental degradate is persistent. • Environmental degradate has low soil binding potential. • Degradate is detected in water monitoring studies.	• Parent compound has low toxicity relative to expected exposures. • Metabolite/degradate found in only one matrix at 10-20% of the total residue (unless that matrix is a major human food). • Metabolite/degradate present at very low residue levels (in mg/kg). • Metabolite/degradate structure is similar to innocuous chemicals • Metabolite/degradate occurs predominantly in animal feeds rather than commodities that are human foods. • Hydrophilic metabolites less toxic than the parent compound **Considerations for drinking water:** • Environmental degradate is short-lived. • Environmental degradate has high soil binding potential. • Degradate is not detected in terrestrial field dissipation studies.

Table 2. Considerations for Major (>10% of the TRR) Metabolites to be Included in the MRL/Tolerance Expression

More likely to be included	Less likely to be included
• Multi-residue methods are able to recover and detect metabolite. • Concentrations of metabolites in commodities are likely to be much greater than the parent compound. • Metabolite likely to be found in commodities that are human foods. • Parent is not expected to be found and is therefore not a suitable marker compound. • Levels of metabolite adequate to serve as an indicator of misuse. • Parent compound is highly toxic and metabolite/degradate likely to cause toxicity through same mechanism of action.	• Metabolite cannot be determined by multi-residue methods, while parent can be recovered. • Found in only one matrix at 10-20% of the total residue. • Parent compound has very low toxicity (i.e., ADI or RfD is very high). • Metabolite does not warrant inclusion on toxicological grounds. • Metabolite is naturally occurring • Metabolite originates from other sources, e.g. other pesticides or industrial chemicals.

Principles for Establishing a Residue Definition for Setting MRLs/tolerances

26. The definition of residues for MRL/tolerance enforcement purposes should be as practical as possible and preferably based on a single residue component as an indicator of the total significant residue - the parent compound, a metabolite, or a derivative produced in an analytical procedure. The selected residue component should reflect the application condition of the pesticide (dosage rate, pre-harvest interval) and it should be quantified by a multi-residue procedure whenever possible. Monitoring for additional residue components only adds to the cost of analyses. As a general rule the analytical methods submitted must be specific enough to determine all components included in the residue definition in order to enforce established or provisional MRLs. In general, residue definitions based on a common moiety, which would also require a common moiety analytical method, should be avoided. If it cannot be avoided in order to determine a moiety common to two or more active ingredients or significant, major metabolites, then an unspecific method of analysis is acceptable (see example below for dithiocarbamates).

27. The advantage of this approach is appreciable as overall costs can be reduced and many more samples may be analysed by the regulatory laboratories. In addition, more laboratories can participate in regulatory monitoring of residues, since a relatively simple and rapid analytical procedure may not require the expensive equipment and time necessary for an extensive determination of all components of a residue. Nevertheless, the expression of residues for MRL enforcement as a single compound does not reduce the data requirements. Complete information on the total residue composition and the relative ratio of residue components is needed to determine whether a single compound can also be used for risk assessment purposes. Where possible, this information should be derived from the quantitative magnitude of the residue studies that are most relevant to the GAP conditions. Otherwise, the ratios seen in the most relevant timings for metabolism studies should be used. If appropriate ratios can not be proposed from studies (due to significant variation in the levels of various metabolites across crops), then it may not be possible to deduce separate residue definitions for risk assessment and MRL enforcement purposes. The following examples illustrate the complexity of deriving a residue definition for MRL setting.

1. Several pesticides are metabolized to a compound, which itself is used as a pesticide (example: benomyl → carbendazim), and in some cases, the toxicology is substantially different for the pesticide and the metabolite (example: dimethoate → omethoate). Whenever possible, the parent pesticide and its metabolite(s) used as pesticides should be subject to separate MRLs. Analysing food commodities in trade for the metabolite may provide no information on which compound was used.

2. Where it is not possible to set separate MRLs because the parent pesticide is degraded rapidly or an analytical method is not available for measuring and distinguishing the parent compounds (examples: ethylene-bis-dithiocarbamates, benomyl → carbendazim), the MRLs applying to the pesticides concerned can only be determined in terms of the metabolite(s) or transformation products.

3. Another problem occurs when the metabolite from a pesticide may also originate from sources other than use of the pesticide. In this case, a residue of the metabolite present in a sample cannot unequivocally be traced back to its origin, and therefore the metabolite should not be included in the residue definition for the MRL (examples: cyromazine → melamine; and prometryne → melamine).

28. As far as possible the same definition of residue should apply to all commodities, although there are exceptions. For example, if the major residue in livestock commodities is a specific animal metabolite, a definition, which includes that metabolite, is needed for MRL enforcement. However, the animal

metabolite is not required in the residue definition for crop commodities if it is not found in the crops. Separate definitions would then be proposed for commodities of plant and animal origin.

29. The following examples are taken from the 2002 FAO manual on the submission and evaluation of pesticide residue data and other publicly available evaluation reports.

Scenario 1: Expression of the residue in terms of the parent compound

It is generally preferable to express a residue in terms of the parent compound. Even if the residue consists mainly of a metabolite, the residue should be expressed in terms of the parent pesticide after molecular weight adjustment. Some examples are given to illustrate the practical application of the principle. If the parent compound can exist as an acid or its salts or a base or its salts, the residue is preferably expressed as the free acid (e.g., RCOOH) or free base (e.g., RNH_2).

Examples:

Residue definition of 2,4-D: sum of 2,4D, its salts and esters expressed as 2,4 D

Residue definition of methiocarb: sum of methiocarb, its sulphoxide and its sulphone, expressed as methiocarb

Scenario 2: Expression of the residue in terms of the parent compound without weight adjustment

No allowance was made for molecular weights in the definitions of residues of some older compounds. Because such definitions are widely accepted the need for change should be carefully considered. The best time for the reconsideration of an existing residue definition is during a periodic review/re-evaluation.

Examples:

Residue definition of DDT: sum of p,p'-DDT, o,p'-DDT, p,p'-DDE and p,p' TDE (DDD)

Residue definition of heptachlor epoxide: sum of heptachlor and heptachlor epoxide.

Scenario 3: Quantitative conversion from parent into another chemical entity:

If the parent compound is quantitatively converted to another chemical entity by the analytical method, the residue is preferably expressed as the parent.

Residue definition of aluminium phosphide: phosphine (hydrogen phosphide, IUPAC: phosphane)

Scenario 4: Conversion of metabolites and parent compound into a single compound in the analytical method

If metabolites are known to be present in significant amounts but the analytical method measures the total residue as a single compound, the residue is expressed as the parent compound. The metabolites included in the residue should be listed, if feasible.

Example:

For the quantification of fenthion residues, parent compound, its oxygen analogue and their sulphoxides and sulphones are all oxidized to a single compound (fenthion oxygen analogue sulphone).

Residue definition of fenthion: sum of fenthion, its oxygen analogue and their sulphoxides and sulphones, expressed as fenthion

Scenario 5: Lack of specific methodsfor the residue definition for enforcement purpose.

Ideally it should be possible to measure the residue as defined, with a LOQ adequate for proposed MRLs, with a high degree of specificity by a multi-residue analytical method. Although circumstances may warrant exceptions, the definition of a residue should not normally depend on a particular method of analysis. However, in the case of dithiocarbamates it is necessary to describe the residue as ".... determined and expressed as ..." to produce a practical definition for residues.

Example:

Residue definition of mancozeb for compliance with MRLs*:* total dithiocarbamates, determined as CS_2 and expressed as mg CS_2/kg

Scenario 6: Metabolites arising from different sources

These metabolites should generally be excluded from definitions of residues for enforcement purposes unless the definition is a combined one covering the various sources. For example, p-nitrophenol arises from both parathion and parathion-methyl. It is often a major component of aged residues but is not included in the definitions of the residues.

Where a metabolite of one pesticide is registered for use as a second pesticide, separate MRLs would normally be established if the analytes of the two compounds were different. Preferably no compound, metabolite or analyte should appear in more than one residue definition.

Example:

Triadimenol is a registered pesticide and a metabolite of triadimefon. The MRLs for triadimefon are for triadimefon only. The MRLs for triadimenol are for triadimenol only, but cover triadimenol residues arising from the use of either triadimefon or triadimenol.

Scenario 7: Metabolites arising from different sources of quickly metabolized parent compounds

There are cases of pesticides, however, where the chemical instability of the parent compound or the limitations of analytical methodology do not allow the application of the above principle. In such cases the residue definition has to be based on the stable common moiety.

Example:

Benomyl and thiophanate-methyl both degrade to carbendazim.

- **Residue definition of benomyl:** sum of benomyl and carbendazim, expressed as carbendazim

- **Residue definition of carbendazim: carbendazim**

- **Residue definition of thiophanate-methyl**: sum of thiophanate-methyl and carbendazim, expressed as carbendazim; overall: sum of benomyl, carbendazim, and thiophanate-methyl, expressed as carbendazim

Notes: *Benomyl*: Residues arising from the use of benomyl are covered by the MRLs for carbendazim.

Carbendazim: MRLs cover carbendazim residues occurring as a metabolic product of benomyl or thiophanate-methyl, or from direct use of carbendazim.

Thiophanate-methyl: Residues arising from the use of thiophanate-methyl are covered by the MRLs for carbendazim.

Scenario 8: Bound residues and conjugates

A major part of the residue of some pesticides is difficult to extract ("bound"; requires rigorous extraction methods such as microwave, heated acid or base extractions) or conjugated, with the free residue disappearing very quickly. The "bound" or conjugated residue therefore may be a better indicator for MRL enforcement. However, in situations where conjugated or bound residues are expected to be present along with the corresponding free residues, consideration should be given as to whether the residue definition for MRL enforcement purposes can be based on the simpler methodology that does not include a hydrolysis step (e.g., as done for bendiocarb residues in plants in example below). In such cases a suitable conversion factor from monitoring to risk assessment may be needed to account for the bound or conjugated residues.

Example:

Residue definition of bendiocarb

- plant products: unconjugated bendiocarb
- animal products: sum of conjugated/unconjugated bendiocarb, 2,2 dimethyl-1,3-benzodioxol-4-ol/N-hydroxymethyl-bendiocarb, expressed as bendiocarb.

The previous example for bendiocarb illustrates residue definitions using just free/unconjugated residue (plants) as well as both conjugated and unconjugated residues (animal products).

Scenario 9: Residue definition in case of polar metabolites:

It is not always necessary to include hydrophilic metabolites even if they are major in terms of quantitative occurrence into the DoR (e.g. hydroxylation or conjugation to a hydrophilic moiety is a common mechanism of detoxification).

Examples:

Glyphosate: The main metabolite of glyphosate in soybean and in some genetically modified glyphosate-tolerant corn varieties is aminomethyl phosphonic acid (AMPA). As for estimation of dietary intake and the risk assessment component relating to exposure, the 2004 JMPR concluded that AMPA was of no greater toxicological concern than its parent compound.

Definition of glyphosate residue (for compliance with MRLs): glyphosate

Definition of glyphosate residue (for estimation of dietary intake): sum of glyphosate and AMPA, expressed as glyphosate.

Pyrasulfotole:

The residue definition for pyrasulfotole is parent and the pyrasulfotole desmethyl metabolite, expressed as pyrasulfotole. Pyrasulfotole desmethyl is included as it occurs in plant commodities at the same order of magnitude and might be of similar toxicity. As the ratio between pyrasulfotole and its desmethyl metabolite can vary, the DoR comprises the sum of parent compound and metabolite (pyrasulfotole and pyrasulfotole-desmethyl (including conjugates), expressed as pyrasulfotole) for MRL setting and for dietary exposure assessment Pyrasulfotole benzoic acid is the prevalent metabolite in plant commodities, but based on the toxicological evaluation of this metabolite, it is not necessary to include it in the DoR for risk assessment or MRL setting.

Scenario 10: Separate residue definitions for risk assessment and for enforcement

As noted in the introduction, for some compounds it may be necessary to establish separate residue definitions for MRL setting and for risk assessment. The following are examples of this situation, where a single marker compound is selected as the analyte for MRL setting and compliance purposes, but a more complex definition may be appropriate for risk assessment.

Examples:

Residue definition of bitertanol in animal commodities:

- for MRL setting: bitertanol
- for dietary risk assessment: sum of bitertanol, p-hydroxybitertanol, and the acid-hydrolysable conjugates of p-hydroxybitertanol, expressed as bitertanol.

Residue definition of tolylfluanid in plant commodities:

- for MRL setting: tolylfluanid
- for dietary risk assessment: sum of tolylfluanid and DMST [N,N-dimethyl-N-(4-methylphenyl) sulfamide], expressed as tolylfluanid

Scenario 11: Separate residue definitions for plant and for animal commodities

Quite often separate residue definitions need to be established for plant and for animal commodities for risk assessment as well as for enforcement.

Residue definition of chlorothalonil for enforcement purposes:

- for commodities of plant origin: chlorothalonil
- for commodities of animal origin: 4-OH-2,5,6-trichloroisophthalonitrile, expressed as chlorothalonil equivalents.

Residue Definition for MRL Setting and Risk Assessment in the Case of Isomers

30. A rough estimation showed that at least 10 % of the active ingredients contain one or more asymmetric carbon atoms. One should also bear in mind that it is possible that isomers degrade in different ways. Therefore, consideration needs to be given to how residue definitions for risk assessment and MRL setting address the presence of isomer mixtures. In practice the starting point in authorising plant protection products is normally the mixture of isomers where all metabolites should be found and taken into account. However, toxicological considerations as well as metabolism should be taken into account as to whether isomers need to be specially considered.

31. For decision making the following points should be taken into account:

1. Enantiomers, diastereomers and cis-trans isomers

   The kind of isomers should be clarified first. According to IUPAC Rules Section E (G. P. Moss, 1996) the following applies:

   Stereoisomers are isomers that possess identical constitution, but which differ in the arrangement of their atoms in space. One differentiates between enantiomer, diastereoisomer, cis-trans isomers.

   1. Enantiomer is one of a pair of molecular entities which are mirror images of each other and non-superposable.

   2. Diastereoisomers (or diastereomers) are stereoisomers not related as mirror images. Diastereoisomers are characterised by differences in physical properties, and by some differences in chemical behaviour towards achiral as well as chiral reagents.

   3. cis-trans Isomers (obsolete synonym: geometric isomers) are stereoisomeric olefins or cycloalkanes (or hetero-analogues) which differ in the positions of atoms (or groups) relative to a reference plane: in the cis-isomer the atoms are on the same side, in the trans-isomer they are on opposite sides.

2. Enantiomers

   In the case of enantiomers, it is difficult to resolve the two substances. It may be possible to separate enatiomers; i.e., in case of methods of analysis by using, for example, chiral columns. Currently, this is not used on a regular basis in routine laboratories.

3. Diastereomers and cis-trans isomers

   For mixtures of diastereomers, the different diastereomers are normally resolved in chromatograms using conventional methods of analysis. Nevertheless, there are cases where this might not be the case. The same applies to cis-trans isomers like permethrin.

   1. Stability of isomers (conversion)

      The decision on setting MRLs for the individual isomers depends also on the stability of the isomers. Cases are known where isomers are not stable in a given matrix. If isomers are converted into each other it makes no sense to establish an MRL for a specific isomer.

2. Level of isomers

The decision to set an MRL for a specific isomer depends on the level of the other isomer in the formulation. In an ideal situation, if it is at a very low level then its contribution to the residue will not be significant and does not have to be taken into account, i.e. no specific MRL has to be set for the other isomer. If however the second isomer is present in significant amounts then a specific MRL may have to be set, taking into account the toxicological properties.

3. Differences in toxicology

The decision on setting specific MRLs for the individual isomers depends also on the effects found in toxicological studies. If these studies show differences connected to the different isomers, this could have an effect on the risk assessment.

32. Situations to be handled are:

1. Single mixture of isomers

As long as a single product comprised of a mixture of isomers is on the market it makes no sense to set specific MRLs for all the different isomers, since the observed effects are connected in the first instance to all isomers.

An example of a single product comprised of a mixture of two isomers is mevinphos, Codex Committee on Pesticide Residues (CCPR) number 53:

Mevinphos, Sum of (E)- and (Z)-mevinphos.

2. Different mixtures of isomers

As long as different products comprised of mixtures of isomers are on the market and no differences in toxicology between isomers are observed, it makes no sense to set specific MRLs for all the different isomers since risk assessment will normally be based on the sum of the effects even if the observed effects could be associated with a specific isomer. If, however, differences in toxicology are seen, then the setting of specific MRLs for all the individual isomers is recommended. Case-by-case decisions should be taken.

An example of different mixtures on the market is cypermethrin, CCPR number 118: Cypermethrin (sum of isomers) (fat-soluble) – Cypermethrin and alpha-cypermethrin have been evaluated for toxicology by the Joint FAO/WHO Meeting on Pesticide Residues in the year 2006

3. Single isomers

As long as only a single isomer is on the market and conversion to other isomers does not occur after application, it is recommended to set a specific MRL for this isomer. Note: since there is no need to enforce other isomers it makes no sense to develop specific methods of analysis for all the different isomers since the residues can be enforced by a non-specific method.

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ANNEX 1

DATABASES ON TOXICOLOGY

This annex provides information on the toxicological databases which can be searched for information on pesticide metabolites and degradates.

Entrez PubMed refers to a life sciences search engine which is available through the U.S. National Library of Medicine (NLM) at http://www.ncbi.nlm.nih.gov/Entrez/index.html.

Also available from NLM is **TOXNET**, a cluster of databases on toxicology, hazardous chemicals, and related areas (http://toxnet.nlm.nih.gov).

From the TOXNET database (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?ToxNetDBDesc.htm) one can search the following databases:

HSDB – Hazardous Substances Data Bank - Broad scope in human and animal toxicity, safety and handling, environmental fate, and more. Scientifically peer-reviewed.

IRIS – Integrated Risk Information System - data from the EPA in support of human health risk assessment, focusing on hazard identification and dose-response assessment.

GENE-TOX – Peer-reviewed mutagenicity test data from the EPA.

CCRIS – Chemical Carcinogenesis Research Information System - carcinogenicity, mutagenicity, tumor promotion, and tumor inhibition data provided by the National Cancer Institute.

TOXLINE – Extensive array of references to literature on biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals.

DART/ETIC – Developmental and Reproductive Toxicology and Environmental Teratology Information Center - Current and older literature on developmental and reproductive toxicology.

Another useful web site is that of the National Toxicology Program (NTP). Their Technical Reports may be especially useful sources on carcinogenicity testing results. http://ntp-server.niehs.nih.gov

Additional information can be found at the Registry of Toxic Effects of Chemical Substances (RTECS), available from the National Institute of Occupational Safety and Health (NIOSH) at: www.cdc.gov/niosh/rtecs.html.

Some information may be found in the opinions of the scientific panel on plant health, plant protection products and their residues (PPR) of the European Food Safety Authority at: http://www.efsa.eu.int/science/ppr/ppr_opinions/catindex_en.html.

Another source might be the European Joint Research Center, especially the European Chemicals Bureau (ECB) and its European Chemical Substance Information System at http://ecb.jrc.it/.