EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Safety of the Food Chain

Pesticides and Biocides

SANCO/11188/2013
Rev. 2, 14 September 2015

Guidance document on criteria for the inclusion of active substances into Annex IV of Regulation (EC) N° 396/2005.

CONTENTS

1. Legal Background

Article 5 of Regulation (EC) No 396/2005 of the European Parliament and of the Council on Maximum Residue Levels for pesticides foresees the establishment of Annex IV, containing a list of active substances for which maximum residue levels (MRLs) are not required.

The general principles for the establishment and update of Annex IV are laid down in Article 5 of Regulation (EC) No 396/2005, which requires that for an active substance which shall be included in Annex IV account should be taken of

- the use of the active substance;
- the scientific and technical knowledge available;
- the result of an assessment of any potential risks to consumers with a high intake and high vulnerability and, where appropriate, to animals;
- the results of any evaluations and decisions to modify the use of plant protection products.

Furthermore, also according to Article 5 of Regulation (EC) No 396/2005, measures to list active substances in Annex IV shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 45(4).

None of the articles in Regulation (EC) No 396/2005 provides for clear decision making criteria regarding inclusion of active substances in Annex IV of that regulation.

2. Criteria for inclusion of an active substance in Annex IV

Five criteria can be defined to include active substances in Annex IV. A decision tree implementing these criteria is depicted in figure 1.

2.1. <u>The active substance is approved as a basic substance under Regulation (EC) No 1107/2009 (Criterion 1)</u>

Article 12 of Regulation (EC) No 396/2005 lays down a procedure for the assessment of existing MRLs by EFSA. Article 12(1) provides for the review of existing MRLs following the approval or non-approval of a substance on the basis of Article 13(2) of Regulation (EC) No 1107/2009. Article 23 of Regulation (EC) No 1107/2009 provides the criteria for the approval of active substances as basic substance. Upon approval, basic substances are included in Part C of the

Annex to Implementing Regulation (EU) No 540/2011 which lists all approved active substances. Therefore Article 12 of Regulation (EC) No 396/2005 applies as well to basic substances as these substances are included in this Annex as active substances just as the other chemicals.

Basic substances are by definition substances of no concern which do not have an inherent capacity to cause adverse effects on humans such as endocrine disrupting (according to the interim criteria in Regulation (EC) No 1107/2009), neurotoxic or immunotoxic effects. So, when approved under Regulation (EC) No 1107/2009, a basic substance is also an implicit candidate for inclusion in Annex IV of Regulation (EC) No 396/2005.

2.2. The compound is listed in Annex I of Regulation (EC) No 396/2005 (Criterion 2)

Active substances, which fulfil the criteria of a `foodstuff` as defined in Article 2 of Regulation (EC) No 178/2002, and are listed as a food or feed commodity in Annex I of Regulation (EC) No 396/2005, are candidates for inclusion in Annex IV. This criterion only applies to the unprocessed food or feed or to food and feed items that were subject to a simple mechanical processing or purification (i.e. milling, grinding,…).

Careful consideration should be given to the appropriateness of including food and/or feed items into Annex IV which are known allergens. In such cases, a consumer exposure risk assessment might be warranted (see criterion 4).

Food and feed ingredients should be considered as chemicals that may have unwanted properties as any other chemical. This is also the case for naturally occurring substances. In addition, food and feed ingredients are used in a purified state while this is not the case when still being part of natural food and feed commodities. Therefore, these substances can only be included in Annex IV if one of the subsequent criteria, given in the following chapters, is fulfilled.

2.3. The compound has no identified hazardous properties (Criterion 3)

2.3.1. Micro-organisms

In practice, today, no ADI or ARfD are defined for micro-organisms approved under Regulation (EC) No 1107/2009. In the toxicological section of the Draft Assessment Report (DAR) it is usually mentioned that:

"In the absence of any significant evidence for toxicity, pathogenicity or infectivity of "*the micro-organism*" in animal studies it was neither possible nor necessary to establish an ADI or an ARfD."

In practice the main condition to approve a micro-organism, is that this organism is sufficiently well defined (at the lowest level possible of strain) to establish that it has no toxicity or infectivity to humans, and that it does not produce/contain any toxin/secondary metabolite that could adversely affect consumer health.

The report of the joint OECD/KemI/EU Workshop on "Microbial Pesticides: Assessment and Management of Risks" (17 - 19 June 2013, Saltsjöbaden, Sweden) recommends as default that no MRL for micro-organisms is to be fixed. If it is shown that a toxic metabolite is produced/present in the product as applied, additional information and/or studies may be needed.

So, when approved under Regulation (EC) No 1107/2009, a micro-organism is also an implicit candidate for inclusion in Annex IV of Regulation (EC) No 396/2005.

Micro-organisms included in the QPS (Qualified Presumption of Safety) list of EFSA for micro-organisms are candidates for possible inclusion in Annex IV of Regulation (EC) No 396/2005.

The problem of sensitising properties, which are set as a default in the absence of any relevant study on this subject, has to be considered separately.

2.3.2. Chemicals and natural materials

An active substance could be candidate to Annex IV when it is of very low toxicity. This conclusion should have been drawn by the relevant scientific bodies of the EU. By no means carcinogenic, mutagenic or reprotoxic (CMR) substances (all categories) nor those with potentially endocrine disrupting properties, are eligible candidates for Annex IV inclusion. To fulfil the criterion of very low toxicity, all of the following criteria need to be fulfilled:

- The active substances, including naturally occurring substances, mustfulfil point 5 of Annex II of Regulation (EC) No 1107/2009 [i.e., active substances that do not show any of the following properties: carcinogenic, mutagenic, toxic to reproduction, sensitising chemicals, very toxic or toxic, corrosive, endocrine disruptors, neurotoxic, immunotoxic].

- The active substances and relevant metabolites, must not produce any adverse effect in any of the toxicological studies up to the test guideline limit doses (depending on the guideline, e.g., 1000 mg/kg bw/d, 2000 mg/kg bw or 5 % in feed).

All substances for which an ADI and/or an ARfD are necessary cannot be included in Annex IV, unless they comply with the criteria discussed in section 2.4.

For some naturally occurring active substances materials, no ADI or ARfD were deemed necessary, due to their toxicological properties and their contribution to total exposure compared to other sources than the pesticide use. The absence of toxicological reference doses must not be confused with the situation of no (sufficient) information on toxicological properties. Two different sub-groups are to be considered.

- The natural compound material is simple and well defined in contrast to
- natural materials composed of a varying pattern of compounds, some of which being well defined in terms of their toxicological properties, but others not.

In the first case, the situation is close to the one of micro-organisms. If ADI and ARfD are not relevant or not appropriate for the compound, then the compound is clearly a candidate for inclusion in Annex IV (eg laminarin and sulphur).

The second case mainly concerns plant or animal extracts, raw or in processed form.

In the case of natural compounds, the absence of defined Toxicological Reference Values (TRV = ADI and ARfD) is not the only reason to propose the inclusion in Annex IV, but a link is made with exposure, and sometimes the high level of "natural exposure" is one of the reason of the absence of these TRV. Such natural compounds can be considered as candidates for inclusion in Annex IV if it is considered that the conditions of use would not significantly increase the background level due to the natural occurrence of the substance (see section 2.4).

2.4. The consumer exposure to the compound linked to use as PPP is considered as negligible compared to other uses in the food chain and/or natural background

2.4.1. Natural exposure is higher than the one linked to the use as PPP (criterion 4)

As stated in the former paragraph, the exposure to "natural compounds" both if they are simple and well defined or if they are not well defined is often compared to the "natural" exposure in order to decide that the substance may be included in Annex IV.

In some cases, this conclusion is obvious as it is the case for instance for sulphur, or for ferric phosphate that degrades in phosphates and iron, and in a more general way for endogenous (non-anthropogenic) compounds, which are widely distributed in food commodities and being of low toxicological concern.

In that case, a "weight of evidence" approach may be used, e.g. taking into account that natural exposure is higher than the one linked to use as PPP, to justify inclusion in Annex IV.

In other cases, particularly considering "extracts", it is less clear, when considering that the use as PPP could substantially enhance the natural exposure, and considering also that the absence of toxicological concern is not well established. It is the case for instance of "fenugreek seed powder".

Well defined compounds and analytical markers of these derivates (for instance eugenol which is the main component of "clove oil), even if their toxicity is not negligible, could also be regarded as candidates to be included in Annex IV if consumer exposure is more important via exposure through consumption via the food commodity of which the substance is derived from. It is emphasized that the exposure resulting from the pesticide use of a compound should be compared to the exposure of the natural compound as present in the food commodity and not to the exposure of the unprocessed food item.

In a number of cases similar considerations apply also for food additives and flavourings authorised in food. For example, the use of benzoic acid as food preservative could be taken into account to consider that setting MRLs is not necessary for this active substance. In this case, the pesticide use of the substance only for non-food and non-feed purpose was considered for its inclusion in Annex IV.

2.4.2. No consumer exposure is forecasted linked to the mode of application of the PPP (Criterion 5)

Natural compounds that are not part of the usual diet (natural oral exposure to the compound is not expected) and for which also no consumer exposure is forecasted linked to the mode of application of the active substance are candidates for inclusion in Annex IV. It is clearly the case e. g. for long Straight Chain Lepidopteran Pheromones (SCLP) for which, when used for instance in dispensers or a few single exposure canisters, anticipated exposure is far below any toxicological concern level. In line with this expectation no residue data are available nor needed, and no analytical method is required.

Caution should be given to possible legal uses of these substances in third countries which might lead to consumer exposure. As a consequence, without any statutory residue limit value in place, products treated in such a way could legally be imported into the EU, without any applicable MRL.

2.5. Case-by-case decisions

The above mentioned criteria will not cover all cases. In all cases expert judgement is necessary. On a case by case basis, other active substances may be included in Annex IV under well described circumstances.

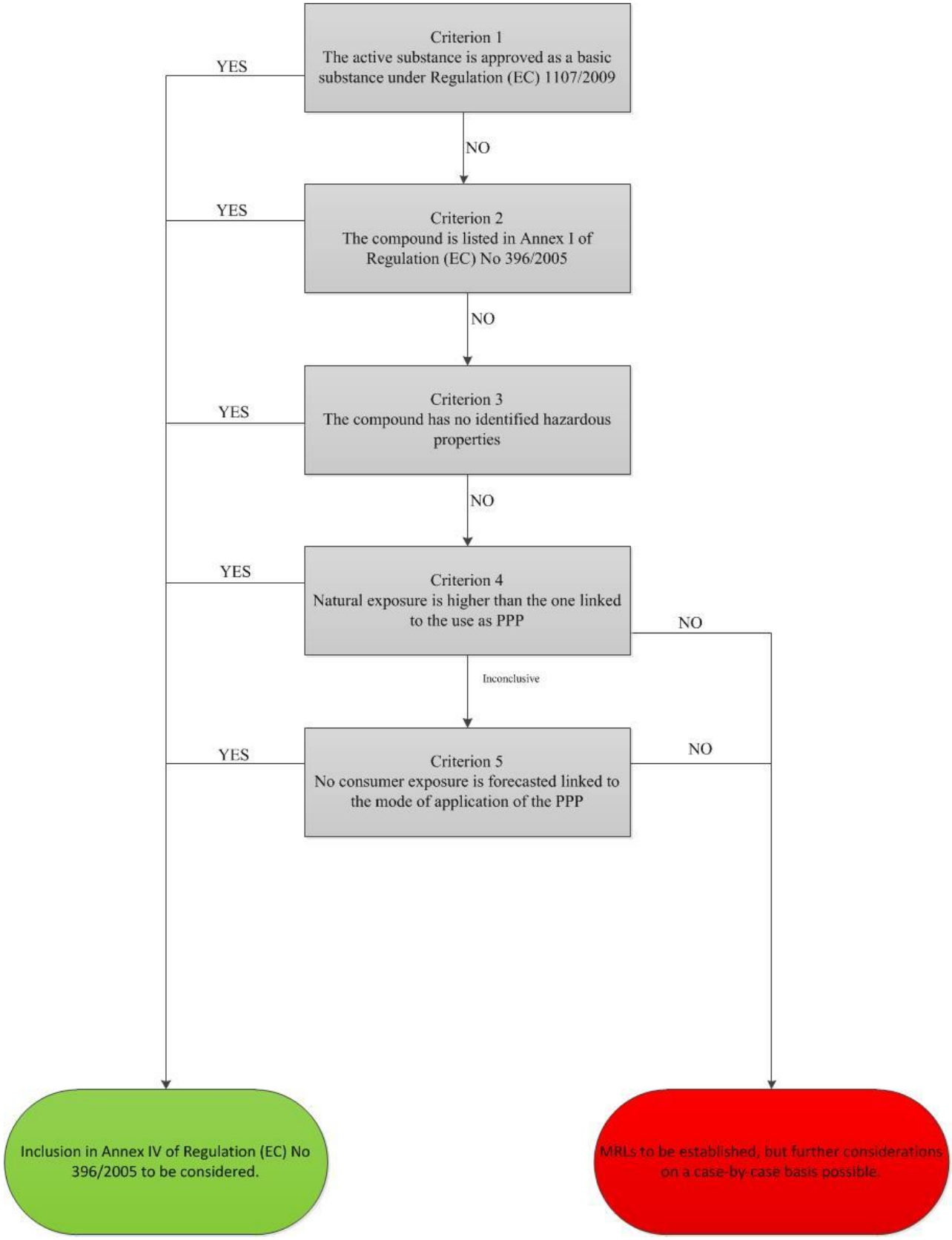

Figure 1: Decision tree for inclusion of an active substance in Annex IV to Regulation (EC) No 396/2005.

3. Implementation of Article 12 of Regulation (EC) No 396/2005 and substances included in Annex IV.

In the following situations the requirement for an evaluation under Article 12 of Regulation (EC) No 396/2005, of substances included in Annex IV of that regulation, could be complied with as follows:

- When a substance is approved as basic substance and is as a consequence included in Annex IV of Regulation (EC) No 396/2005. The decision to amend Annex IV is based on the decision to approve the substance as basic substance pursuant to Article 23 of Regulation (EC) No 1107/2009.

- When a substance is included in Annex IV based on other scientific documents by the EFSA then a conclusion, reasoned or scientific opinion on that substance (eg the Qualified Presumption of Safety (QPS) list from the EFSA in the case of biological agents). The decision to amend Annex IV is then based on that other EFSA document and there is no need to review this decision in the framework of Article 12 provided that the other scientific document provides an assessment equivalent to an EFSA conclusion, reasoned or scientific opinion.

For other substances included in Annex IV, the decision whether an Article 12 opinion is still needed, can be taken on a case-by-case basis taking into account all available information.

4. Conclusion

It appears that inclusion in Annex IV is often not a clear-cut decision but rather has to be based on "expert judgment" to a considerable extent. It appears that it is possible to define 3 groups of candidates for inclusion in Annex IV (considering also a case by case basis approach under well described circumstances):

- **Active substances of no toxicological concerns (see criterion 1 and 3).** This group consists of the active substances that fulfil all of the following criteria: ADI and ARfD are not needed, they are low risk substances [in the meaning of point 5 of Annex II of Regulation (EC) No 1107/2009] and they do not produce any adverse effect up to test guideline limit doses. Active substances for which exposure via usual diet is higher than the one through the use as PPP might also fall into this category. This group may include micro-organisms and basic substances proposed to be approved under Regulation (EC) No

1107/2009, and some well defined compounds for which consumer exposure to the compound or its degradates via usual diet is higher than the one through use as PPP (sulphur, ferric phosphate, case of extract from "high level of consumption foods"). In that case, no more information on residues in registered uses in EU is necessary.

- **Active substances that are food themselves or components of food (see criterion 2 and 4)**, which exhibit a higher natural background levels in food than is expected from PPP use(s), e.g. mint oil. The extent of uses affects the level of exposure of consumers. It would therefore be advisable to establish a system keeping track of proportions of "natural" intake vs. PPP contributions to exposure to maintain justification that PPP contribution is playing a minor role in total dietary intake.
- **Active substances that are not supposed to be present in foods (see criterion 5)**, due to their mode of application. In that case, the rationale for inclusion in Annex IV would be a "no exposure" situation for food, having been produced in EU. In this case attention should be paid to the following possibility: other uses might occur in third countries leading to significant consumer exposure, meaning that without any statutory limit value in place, products treated in such a way could legally be imported into the EU.

ANNEX I

EFSA (2007) recommendations

In the reasoned opinion "First establishment of Annex IV of Regulation (EC) 396/2005 -28 October 2007[1]", EFSA presented different "general statements" concerning risk assessment, and pointed out some specificities of Annex IV candidates:

"In general, the risk is a function of the hazard and the probability of the occurrence of the hazardous event. In consumer risk assessment of pesticide residues the probability of the hazardous event is related to the oral exposure to the agent via food. The risk assessment process should provide a scientific characterization of the risk in a qualitative and quantitative way. A health risk is expected if a compound has certain hazardous properties and where an exposure occurs at a level which causes a biological response. In order to assess the risk, it is therefore necessary to identify and characterize the possible hazards and to estimate the likelihood and magnitude of the exposure.

Risk assessment is a process which is divided into four separate steps, the hazard identification, the hazard characterization, the exposure assessment and finally the risk characterization.

For identification and characterization of the hazard of a chemical active substance or microbiological pest control agent (MPCA), a range of toxicological studies, as specified in the pesticide legislation, is assessed. As a result, a hazard classification is proposed and toxicological reference values (acceptable daily intake- ADI and acute reference doses - ARfD) are established.

For the exposure assessment, the dietary intake is estimated by using specific models which take into account food consumption and the expected residue levels. The expected residue levels are estimated from supervised field trials carried out according to the critical agricultural practice. In certain cases, also monitoring data might be used in the exposure assessment.

Finally, the calculated exposure is compared to the toxicological reference values. If the intake amounts for less than the reference values, the risk is considered acceptable. If the reference

[1] EFSA Scientific Report (2007) 115, 1-161

values are exceeded the consumer health risk is considered as unacceptable as potential negative effects cannot be excluded. In cases where both the hazard and exposure are proved to be very low, the consumer risk can be considered as low or even negligible. However, it should be pointed out that a distinction of "low risk", "acceptable risk" or "unacceptable risk" is not always that clear, since the borderlines between the three cases are affected by a number of uncertainties (e.g. exposure model and data uncertainties).

In Figure 1, a simplified graphical representation of the relation between hazard and exposure with regard to consumer risk is given.

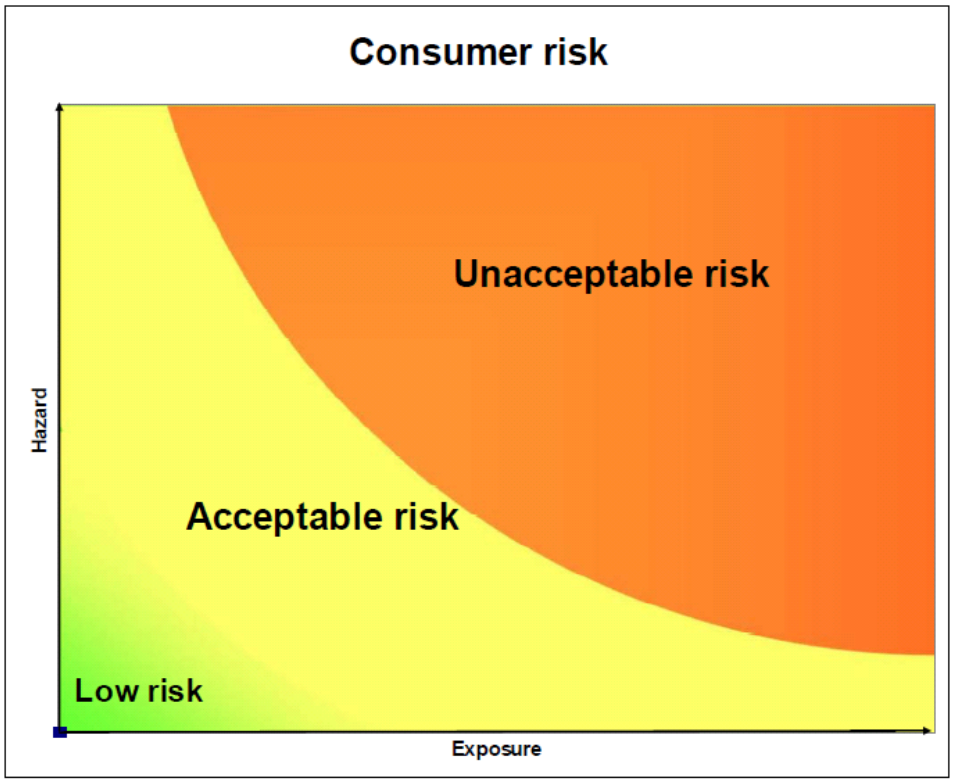

Figure 2: Relation of hazard and exposure with regard to consumer risk from pesticide residues in food.

Although no agreed criteria are yet established, it is EFSA's view that only substances which are likely to present a low consumer health risk should be considered for inclusion in Annex IV of Regulation (EC) 396/2005. In particular, the consumer health risk, associated with the use of the active substance according to the authorized uses, is considered low if:

- low toxicity is observed in the toxicity studies and
- no or a low potential dietary exposure is expected.

The assessment described in the following section will therefore focus on the following main questions:

- What were the conclusions of the peer review, in particular with regard to toxicological reference values and classification of the active substance?
- What is the magnitude of the expected exposure for the representative uses assessed in the peer review?
- Are the currently authorized uses comparable with the representative uses assessed in the peer review, regarding the occurrence of residues in treated crops?
- Does the use of the pesticide according to the currently authorized GAP represent a low risk situation?

This risk assessment exercise is mainly based on the documents generated during the peer review of the active substances in the framework of Directive 91/414/EEC and 1107/2009 and the information provided from Member States regarding the uses authorized at national level.

> It should be stressed that the conclusions in this report are only valid for the assessed uses. If the use pattern will be extended to other uses which have not been assessed, further evaluations will be necessary as to whether acute or/and chronic exposure will significantly increase. The conclusions have to be reconsidered also if new information on other aspects relevant for the risk assessment becomes available. For microorganisms, special consideration should be given to technical and scientific developments. In particular, the scientific progress concerning the production and identification of metabolites/toxins should be followed."