Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Tank mixes in the authorisation procedure for plant protection products

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1 Introduction

This is the second edition of the concept for tank mixes in the authorisation procedure. This new version contains updated references to the legal basis and, above all, additional new data requirements for exposure estimation concerning operators, workers, bystanders and residents.

Tank mixes (TM) are used in agriculture and forestry to achieve, for example, a broader spectrum of activity, to prevent a development of resistance in populations of harmful organisms, to reduce the number of working steps or because products can only be mixed shortly before application due to certain physico-chemical properties.

This document differentiates between untested and tested TMs. Untested TMs are used in practice, for example due to advice which has been given or based on the operator's own experience, without having been tested in the context of the authorisation procedure. The instructions for use often state such mixes.

Tested TMs on the other hand are evaluated by the authorities during the regular authorisation procedure and are declared as such. An application must be submitted by the applicant for this kind of TM. As far as tested TMs are concerned, according to Regulation (EC) No 546/2011 implementing Regulation (EC) No 1107/2009, a distinction is made between recommended tank mixes (ETM) and required tank mixes (VTM).

This document only addresses those TMs which are subject to the authorisation procedure. The requirements for submitting applications and the test and data requirements for TMs are shown in the context of the authorisation procedure for the various test areas, and statements with regard to labelling and the placing on the market of tested TMs are made. The document applies to all regular authorisation procedures according to Regulation (EC) No 1107/2009.

Substances which are not subject to plant protection regulations but are used in (untested) TMs, such as fertilisers, are not taken into consideration here.

2 Legal basis

Regulation (EC) No 1107/2009 of the European Parliament and the Council on the placing on the market of plant protection products and repealing Council Directives 79/117/EEC and 91/414/EEC form the legal basis. The test and data requirements and assessment principles which were described in Directive 91/414/EEC in Annexes II, III and VI, are now included in the following regulations implementing Regulation (EC) No 1107/2009: Regulation (EU) No 283/2013 setting out the data requirements for active substances, Regulation (EU) No 284/2013 setting out the data requirements for plant protection products and Regulation (EU) No 546/2011 as regards uniform principles for evaluation and authorisation of plant protection products[1]. Specific data requirements concerning TMs have neither been laid down in Annex II of Directive 91/414/EEC nor are they provided in Regulation (EU) No 283/2013.

The mentioned Regulations are directly applicable in any EU Member State. The Plant Protection Act defines regulations at national level in Germany. It does not contain any separate regulations for TM.

Art. 29 of Regulation (EC) No 1107/2009 states that the uniform principles of Regulation (EU) No 546/2011 are to be applied for the assessment during the authorisation process of a plant protection product. According to these principles and Article 29 (6), the interactions between active substances, safeners, synergists and co-formulants are taken into consideration when the plant protection product is evaluated. It is postulated that interactions with other plant protection products and their components must be considered in the context of the authorisation procedure in the same way. To be able to judge such effects, additional data may have to be submitted with the application for authorisation. Details on the individual test areas are described in more detail in chapters 5.1 to 5.4.

The uniform principles in Regulation (EU) No 546/2011 differentiate between recommended tank mixes (ETM) and required tank mixes (VTM); a different plant protection product or formulant (=adjuvant)[2] serves as a mixing partner.

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[1] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.

Commission Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market.

Commission Regulation (EC) No 546/2011 of 10.06.2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products.

Concerning the transitional measures implementing Regulation (EC) No 283/2013, due account shall be taken of Commission Regulation (EC) No 1136/2014 of 24 October 2014 amending the Regulation (EU) No 283/2013 concerning transitional measures as regards procedures concerning plant protection products.

[2] Formulant and adjuvant are synonyms. Annex VI of the uniform principles in Directive 91/414/EEC speaks of formulants and Regulation (EC) No 1107/2009 of adjuvants. Implementing Regulation (EU) No 546/2011 still speaks of formulants because Annex VI was adopted one-to-one by Regulation (EC) No 1107/2009.

Part I (chemical plant protection products) of the uniform principles reads:

Regarding recommended tank mixes (ETM):

Point B (evaluation), 2.1.5: *Where the product label includes recommendations for use of the plant protection product with other plant protection products and/or with formulants (=adjuvants) as a tank mix, Member States shall evaluate the appropriateness of the TM and its conditions of use.* An assessment must still be carried out according to Point B (evaluation), 2.7.3 *as to whether the products used for the mixture are chemically and physically compatible.*

Under Point C (decision-making) 2.1.5 it is added that the Member States accept the recommendation if it is well justified.

Regarding required tank mixes (VTM):

Point B (evaluation), 2.1.5: *Where the product label includes requirements for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix, Member States shall make the evaluations referred to in points 2.1.1 to 2.1.4 in relation to the information supplied for the tank mix.*

The corresponding regulations for plant protection products which contain micro-organisms are described in Part II of the uniform principles.

Point B, 2.2.2.4 (special principles) reads:

Where the proposed label claims include requirements or recommendations for use of the preparation with other plant protection products or adjuvants as a tank mix, and/or where the proposed label includes indications concerning the compatibility of the preparation with other plant protection products as a tank mix, those plant protection products or adjuvants must be physically and chemically compatible in the tank mix. Biological compatibility must also be demonstrated for tank-mixtures, i.e. it must be shown that each plant protection product in the mixture performs as expected and that no antagonism occurs.

Point C (decision-making), 2.4.1.5, Part II of the uniform principles reads:

Where proposed label claims include requirements for use of the preparation with other specified plant protection products or adjuvants as a tank mix, the mixture must achieve the desired effect and comply with the principles referred to in points 2.4.1.1 to 2.4.1.4.

Where proposed label claims include recommendations for use of the preparation with specified plant protection products or adjuvants as a tank mix, Member States shall not accept the recommendations unless they are justified.

3 General information on tank mixes in the context of the authorisation procedure

Mixing partners for a TM either to be tested or which has already been tested with a plant protection product can be

- another plant protection product or
- an adjuvant (formulant).

The mixing partners of a plant protection product in a TM must be authorised or approved in Germany. The mixing partners in a TM from another EU Member State which has been authorised by mutual recognition must also be authorised or approved in Germany. The duration of authorisation for a TM depends on the TM partner with the shortest term of authorisation or approval. The same applies for deadlines for using up or selling off existing stocks according to Article 46 of Regulation (EC) No 1107/2009.

It is not sufficient to name an active substance as a mixing partner: a specific plant protection product or adjuvant must be stated as the mixing partner.

In the context of applications according to Article 51 of Regulation (EC) No 1107/2009, only the area of residues has to be re-tested regularly. Other test areas no longer have to be tested if comparable authorised uses with regard to possible effects were reviewed as part of the authorisation procedure according to Article 29 pp of Regulation (EC) No 1107/2009, meaning that data can be extrapolated to the application according to Article 51 of Regulation (EC) No 1107/2009. If extrapolation is not possible, data on risk assessment for operators, workers and uninvolved third parties and the natural balance may also be necessary according to Article 51.

TM are described at use level. Therefore, some uses of authorised plant protection products can serve as TMs and others not. The uses of one plant protection product can be authorised as VTMs and others as ETMs. Also, the uses of the TM can be different to the uses of the mixing partners which have been authorised singly.

All restrictions which apply to the mixing partners also apply to TMs. When using ETMs, the strictest restriction out of all the mixing partners applies, providing there are no special restrictions which apply to the ETM. As far as VTMs are concerned, special restrictions for the TM must always be observed.

4 Submitting applications and issuing notifications for tank mixes

The applicant decides when placing his application whether the TM should be tested as a VTM or an ETM and which mixing partner is intended for the TM. The intended TMs must be stated in the application form including the application rate for the mixing partner. In addition, the purpose of the TM must be described in the instructions for use in the dossier (Doc. M III A 1 Section 7 and in the draft registration report). Applications for TM must be submitted for specific uses.

The text for recommendations for untested mixes, like in instructions for use, must be clearly distinguishable from the text for tested mixes.

If a plant protection product has to be mixed with a mixing partner to fulfil the purpose of the label (e.g. control of a different harmful organism or different timing for control measures or resistance management), this is a VTM and must be clearly distinguished as such in the application for authorisation. An authorised VTM is binding for the practical use of the plant protection product for the specific use. This has consequences for the labelling: the marketing for the product must not be misleading. e.g. two products whose authorisation has no common use must not be packaged together and marketed under a new name.

The applicant who applies for the TM receives an authorisation certificate for the TM and not the owner of the mixing partner stated for the TM. The TM applicant does not have to submit the letter of access from the owner of the mixing partner to the BVL for the authorisation as a TM either. Any letters of access for using studies belonging to the owner of the mixing partner stated for the TM remain unaffected.

5 Test and data requirements for tank mixes for the individual test areas

According to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009, explicit test requirements for TM with regard to their physical and chemical properties, their efficacy and toxicology are listed.

All other data and test requirements stated in the following for TMs, do not emanate explicitly from the regulations laying down the data requirements in Regulation (EC) No 1107/2009 but are specified for evaluation by the authorities involved in authorisation for purely technical reasons when they are needed to make a decision on an individual case. Just as with other applications, certain data may not have to be submitted if these can be extrapolated or if technically justified statements are submitted.

5.1 Physical, chemical and biological properties

All TMs applied for by the applicant are evaluated for their physical, chemical and technical properties. All TMs are also evaluated for the physical, chemical and biological compatibility with other products.

The basis for this is the annex to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products. Part A (Chemical Preparations) of the data requirements for plant protection products under point 2.9 Physical and chemical compatibility with other products including plant protection products with which its use is to be authorised states that *the physical compatibility of recommended TMs must be determined and reported*. *Known incompatibilities shall be indicated.*

In Part B (preparations of micro-organisms, including viruses) of the Annex to Regulation (EU) No. 284/ 2013 setting out the data requirements for plant protection products under point 2.8 Physical, chemical and biological compatibility with other products including plant protection products with which its use is to be authorised, the following compatibility requirements are listed:

- *2.8.1 The physical compatibility*
  The physical compatibility of recommended tank mixes must be determined and reported.
- *2.8.2 The chemical compatibility*
  The chemical compatibility of recommended tank mixes must be determined and reported except where examination of the individual properties of the preparations would establish beyond reasonable doubt that there is no possibility of reaction taking place. In such cases it is sufficient to provide that information as justification for not practically determining the chemical compatibility.
- *2.8.3 The biological compatibility*
  The biological compatibility of tank mixes must be determined and reported. Effects (e.g.

antagonism, fungicidal effects) on the activity of the micro-organism after mixing with other micro-organisms or chemicals must be described. The possible interaction of the plant protection product with other chemical products to be applied on the crops under the expected conditions of use of the preparation shall be investigated, based on the efficacy data. Intervals between application of the biological pesticide and chemical pesticides shall be specified, if appropriate, in order to avoid loss of efficacy.

Although here the Regulation refers partially to *recommended* TMs, the requirements should also apply to VTMs. It is understood that the Regulation defines “recommended” not as the “recommended TM”, but as a recommendation for an application with another product, whereby the requirements naturally also apply to VTM.

Besides the data requirements stated for the mixing partners in the annexes to Regulation (EU) No 284/2013, studies must be submitted and evaluated for the TMs in addition to all the properties relevant to application. For mixes which are applied by spraying (spray tank mixes), evidence must be provided for example concerning the emulsifying or suspension behaviour, dilution stability, wet sieve test and persistent foaming.

5.2 Efficacy

The annex (Part A and Part B) of Regulation (EU) No 284/2013 as regards the data requirements for plant protection products under point 6.2 Testing effectiveness states for the area of efficacy that: *Where label claims include recommendations for the use with one or several other plant protection products or formulants (=adjuvants), information on the performance of the mixture must be provided*. Similarly, point 6.4.1 and point 6.5 Phytotoxicity to target plants (including different cultivars) or to target plant products states that: *Where label claims include recommendations for the use with one or several other plant protection products or formulants (=adjuvants), the previous paragraphs apply to the mixture.*

It must be assumed that evidence must be provided on the effects of ETM mixtures as well. Since Regulation (EU) No 546/2011 differentiates between ETMs and VTMs (see chapter 2, "Legal basis"), VTM requirements must be higher since specific evidence of the effects is requested. As far as ETMs are concerned, only information is required.

According to Regulation (EU) No 546/2011, the appropriateness of ETMs must be examined, this must be well justified, and information on efficacy must be submitted.

Altogether, the following requirements result for the area of efficacy:

In the context of the authorisation procedure efficacy studies must provide evidence for ETMs that the product is also sufficiently effective without the product partner for the specific use applied for. If adequate efficacy in the specific use applied for should only be guaranteed together with the product partner in the mixture, it is a VTM. If, due to the mixing partner, for example the application rate in the specific use applied for is reduced (lower minimum effective dose) in comparison to the application without the mixing partner in the context of authorisation for achieving satisfactory efficacy, this is also a VTM. It must be assumed that

sufficient efficacy cannot be achieved with the product alone at a lower application rate. Subsequently, applications with deviations in the description of correct application (e.g. application rate, spraying date, etc.) which only achieve the intended aim together with the mixing partner fall into the VTM category.

The task of VTM evaluation emanates clearly from the annex to Regulation (EU) No 546/2011. In Part I [chemical plant protection products], B (Evaluation) of the annex to the uniform principles under point 2.1.5, reference is made to point 2.1 Efficacy and points 2.1.1 to 2.1.4 for VTMs.

For example, point 2.1.3 states that the Member States shall evaluate the efficacy data of the plant protection product as provided for in the annex to Regulation (EU) No 546/2011 having regard to the degree of control or extent of the effect desired and having regard to the relevant experimental conditions. In addition, under point 2.2. Absence of unacceptable effects on plants or plant products, point 2.2.3 stipulates: *Where the product label includes requirements for use of the plant protection product with other plant protection products or with formulants (=adjuvants) as a TM, the evaluation as specified in point 2.2.1. shall be carried out by the Member States in relation to the information supplied for the tank mix.* Point 2.2.1 also refers to the data requirements for plant protection products in the area of efficacy.

This means that for VTMs all data requirements according to the implementing regulations of Regulation (EC) No 1107/2009, points 6 pp must be fulfilled, i.e. a complete efficacy evaluation must be carried out.

For plant protection products which contain micro-organisms (Part II of Regulation (EU) No 546/2011 as regards uniform principles), the evaluation of TMs must assume the same data requirements as for chemical plant protection products.

Part II of the uniform principles, B (specific principles), point 2.4.6 states on efficacy data:

Where the label of the plant protection product includes requirements for use of the plant protection product with other plant protection products and/or adjuvants as a tank mix, Member States shall make the evaluations referred to in points 2.4.3 to 2.4.5 in relation to the information supplied for the tank mix. Where the label of the plant protection product includes recommendations for use of the plant protection product with other plant protection products and/or adjuvants as a tank mix, Member States shall evaluate the appropriateness of the mix and its conditions of use.

Part II of the uniform principles, point C (decision-making), point 2.4 on efficacy states:

If the proposed label claims include requirements for the use of the preparation with other specified plant protection products or adjuvants as a tank mix, the mixture must guarantee the desired effect and comply with the principles referred to in 2.4.1.1 to 2.4.1.4.

If the proposed label claims include recommendations for the use of the preparation with other specified plant protection products or adjuvants as a tank mix, these recommendations shall only be accepted by the Member State concerned if they are justified.

Part II of the uniform principles, point C (decision-making) point 2.4.2.7 concerning unacceptable impacts on plants and plant products states:

If the label claims include requirements for the use of the preparation with other specified plant protection products or adjuvants as a tank mix, the mixture must comply with the principles referred to in 2.4.2.1 to 2.4.2.6.

5.3 Fate and behaviour in the environment and ecotoxicology

Current scientific knowledge on ecotoxicological combination effects says that as a rule, exposure to a mixture of substances causes a higher toxicity than exclusive exposure to the corresponding concentrations of the respective mixture components. As a realistic worst case, an additive combination effect without toxico-kinetic and/or toxico-dynamic interactions can be assumed plausible (on the other hand, the regulatory worst case presents a synergistic combination effect as a consequence of such interactions). Accordingly, it must initially be assumed that the use as a TM generally has a negative influence on the environmental impact of the application of the plant protection products contained.

The test area fate and behaviour in the environment is usually covered by active substance data to a large extent. Provided that due to the intended TM the environmental concentrations expected to be estimated (PEC) according to section 9 of the annex (Part A or Part B) of Regulation (EU) No 284/2013 concerning data requests for plant protection products are influenced in the various compartments, additional data may be necessary which allow exposure estimations which are as realistic as possible.

As far as ecotoxicology is concerned, an alternating influence of the mixing partners added to a TM on the effects known to non-target organisms for the individual mixing partners cannot be excluded. A similar phenomenon can be seen when considering the ecotoxicological effects of active substances in comparison to formulations and of products with a single active substance in comparison to combination products with two or more active substances. As a rule, studies with the required or recommended mix (VTM / ETM) are necessary for determining toxicity to certain representative species. This means that basically, the data necessary for the evaluation of preparations according to section 10 of the annex (Part A / Part B) to Regulation (EU) No 284/2013 must be submitted for both types of tank mixes applied for. This data concerns the documentation regarding the impact on groups of non-target organisms, where exposure to the mixture must be assumed. The available data must enable a reliable risk assessment for these non-target organisms. Alternative approaches which draw on prognosis concepts concerning mixture toxicity and/or which limit the experimental data set to only a few bridging studies can be accepted with a convincing scientific justification in the risk assessment, which is submitted for the tank mixture applied for. The use of such data should be considered, in particular with regard to avoiding

additional experimental toxicity tests with vertebrates. The EFSA technical guidance documents summarise recommendations considering such prognosis concepts concerning mixture toxicity, they can be found in Frische et al. (2014): Environmental risk assessment of pesticide mixtures under regulation 1107/2009/EC: a regulatory review by the German Federal Environment Agency (UBA). Journal für Verbraucherschutz und Lebensmittelsicherheit (Journal for Consumer Protection and Food Safety): Volume 9, Issue 4 (2014), Page 377-389.

5.4 Toxicological evaluation of the preparation, operator safety, residue behaviour

Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products sets out the requirements for the assessment of the acute toxicity of plant protection products, the irritant and sensitizing effects, the exposure of operators, workers, bystanders and residents to plant protection products. No distinction is made between ETM and VTM, so that for both types of TMs the set out requirements must be conformed to.

In addition to the toxicological examinations in section 7 of part A (chemical plant protection products), further investigations on the combination of plant protection products are required as regards acute toxicity. Thus, it stipulates that

if the label of the plant protection product includes requirements for use of the plant protection product with other plant protection products and/or adjuvants as a tank mix, it may be necessary to carry out studies for combinations of plant protection products or for the plant protection product combined with an adjuvant. The need to perform supplementary studies shall be discussed with the national competent authorities on a case by case basis, taking into account the results of the acute toxicity studies of the individual plant protection products and toxicological properties of the active substances, the possibility for exposure to the combination of the products concerned with particular attention being paid to vulnerable groups, and available information or practical experience with the products concerned or similar products.

Concerning the necessary exposure data it is required that *if the plant protection product label includes requirements for use of the plant protection product with other plant protection products or with adjuvants as a tank mix, the exposure assessment must also take account of the combined exposure. Due account is also to be taken of cumulative and synergistic effects which must be stated in the dossier.*

An estimation shall be made, using where available a suitable calculation model, in order to permit an evaluation of the operator exposure, bystander, resident and worker exposure likely to arise under the proposed conditions of use. Where relevant, this estimation shall take into account cumulative and synergistic effects resulting from the exposure to more than one active substance and toxicologically relevant compounds, including those in the product and tank mix.

In Part B, point 7.5, (preparations of micro-organisms, including viruses) supplementary studies for combinations of plant protection products are required: *In certain cases it may be necessary to carry out the studies as referred to under points 7.1 to 7.2.3 for a combination of plant protection products where the product label includes requirements for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix. Decisions as to the need for supplementary studies must be made on a case-by-case basis, taking into account the results of the acute toxicity studies of the individual plant protection products, the possibility for exposure to the combination of the products concerned and available information or practical experience with the products concerned or similar products.*

At least one expert opinion is required for the evaluation of residue behaviour on the extent the intended mixing partner influences the level of residues on harvested produce and its decrease with time and whether the set maximum residue levels can be complied with taking into account the intended waiting periods. As long as it cannot be excluded that the application as a TM presents a more critical case than evaluations up until now have shown (e.g. as in the case of substances with known synergistic effects when taken up by the plant), corresponding residue trials with the TM must be submitted. Otherwise, no further residue trials have to be carried out for TMs as long as the necessary studies have been submitted according to the provisions of Regulation (EC) No 1107/2009 or its implementing regulations for the individual active substances, safeners and synergists.

5.5 Table summarising test and data requirements

The following table provides an overview of the test and data requirements for TMs for the various test areas. It also differentiates between ETMs and VTMs. The exact requirements and corresponding justifications can be taken from points 5.1 to 5.4.

Test criterion	ETM	VTM
physical, chemical and biological properties	Data requirements and evaluation apply in full as for individual products. For ETMs (spray tank) additionally according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products, Part A and Part B: - persistent foaming, - suspensibility, - dilution stability, - wet sieve test, - emulsifying behaviour, - phys. and chem. compatibility	Data requirements and evaluation apply in full as for individual products. For VTMs (spray tank) additionally according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products, Part A and Part B: - persistent foaming, - suspensibility, - dilution stability, - wet sieve test, - emulsifying behaviour, - phys. and chem. compatibility

Test criterion	ETM	VTM
Efficacy	Examination of appropriateness based on the justification for the ETM and the information on efficacy. This must also be able to provide information on whether the sufficient efficacy of the individual product can be assumed.	All data requirements according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products Part A and Part B, points 6.x must be fulfilled, i.e. a complete efficacy evaluation will follow.
Fate in the environment and ecotoxicology	Test scope and data requirements according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products as well as for individual products	Test scope and data requirements according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products as well as for individual products
Formulation-toxicology	Requirements according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products, Part A, point 7.1.8 and part B, points 7.1 to 7.2.3.	Requirements according to Regulation (EU) No 284/2013 on the setting of data requirements for plant protection products, Part A, point 7.1.8 and part B, points 7.1 to 7.2.3
Exposure assessment for operators, bystanders, residents and workers	Data requirements and evaluation for ETMs apply in full as for individual products.	Data requirements and evaluation for VTMs apply in full as for individual products.
Residue behaviour	At least one expert comment is necessary regarding the extent to which the intended mixing partner influences the level of the residues on harvested produce and their decrease with time, and whether the respective set maximum residue level is feasible. As long as it cannot be excluded that the application as a TM presents a more critical case than evaluations have shown up until now, corresponding residue studies with the TM must be submitted.	At least one expert comment is necessary regarding the extent to which the intended mixing partner influences the level of the residues on harvested produce and their decrease with time, and whether the respective set maximum residue level is feasible. As long as it cannot be excluded that the application as a TM presents a more critical case than evaluations have shown up until now, corresponding residue studies with the TM must be submitted.