

Commission Regulation (EU) 2018/782 of 29 May 2018
establishing the methodological principles for the risk
assessment and risk management recommendations referred to
in Regulation (EC) No 470/2009 (Text with EEA relevance)

Article 1	Subject matter
Article 2	Definitions
Article 3	Entry into force
	Signature

ANNEX I

Methodological principles for the scientific risk assessment
referred to in Article 6 of Regulation (EC) No 470/2009

- I. GENERAL PRINCIPLES
 - I.1. Safety and residue tests for the establishment of maximum residue...
 - I.2. Use of experimental animals in safety and residue tests shall...
 - I.3. Documentation presented in relation to safety and residue tests shall...
 - I.4. Where applicable, all observed results from the studies submitted shall...
 - I.5. Test reports shall include the following information (where applicable):
 - I.6. Biological substances other than those identified in Article 1(2)(a) of...
 - I.7. For chemical-unlike biological substances, a report describing the scientific basis...
 - I.8. Certain aspects of the data to be submitted in support...
 - I.9. The general principles for the derivation of MRLs for biocidal...
- II. SAFETY FILE
 - II.1. A full safety data package as described in this section...
 - II.2. Where relevant and high quality literature data where all the...
 - II.3. If data are not provided for standard endpoints, thorough justification...
 - II.4. Detailed and critical summary
 - II.4.1. A detailed and critical summary of the safety file shall...
 - II.4.2. The detailed and critical summary shall:
 - II.4.3. Annexes to the detailed and critical summary shall include:
 - II.5. Precise identification of the substance concerned by the application
 - II.5.1. The data shall demonstrate that the substance has been precisely...
 - II.5.2. Batches used in safety studies shall be identified and adequate...
 - II.5.3. Information on the chemical and physicochemical properties of the substance...
 - II.6. Pharmacology
 - II.6.1. Pharmacodynamics
 - II.6.1.1. Data from the pharmacodynamic studies shall aim to enable the...
 - II.6.1.2. Particular consideration shall be given in relation to pharmacodynamic effects...

- II.6.1.3. Studies relevant to the establishment of a pharmacological ADI shall...
- II.6.1.4. Data on the pharmacodynamic effects of a substance shall:
- II.6.1.5. If pharmacodynamic data are not provided, their absence shall be...
- II.6.1.6. If a pharmacological ADI is not derived, its absence shall...
- II.6.2. Pharmacokinetics
 - II.6.2.1. Pharmacokinetic investigations shall provide information on the absorption of the...
 - II.6.2.2. Metabolites produced in the laboratory animal species shall be compared...
 - II.6.2.3. The pharmacokinetic data obtained from studies in laboratory animals shall...
 - II.6.2.4. Pharmacokinetic data in laboratory animals shall also be used to...
 - II.6.2.5. Pharmacokinetic data may also help to explain unusual results obtained...
- II.6.3. Toxicology
 - II.6.3.1. General principles
 - II.6.3.1.1. Animal studies shall be performed by the oral route since...
 - II.6.3.1.2. Animal studies shall be conducted in established strains of laboratory...
 - II.6.3.1.3. The substance to be tested shall be the active substance....
 - II.6.3.1.4. ICH GL33: Studies to evaluate the safety of residues of...
 - II.6.3.2. Single-dose toxicity, if available
 - II.6.3.2.1. Acute toxicity studies may have been performed for reasons other...
 - II.6.3.2.2. If available, acute toxicity data which may contribute to the...
 - II.6.3.3. Repeat dose toxicity
 - II.6.3.3.1. Repeat dose (90 day) oral toxicity testing
 - II.6.3.3.1.1. Data from repeat dose (90 day) oral toxicity studies shall...
 - II.6.3.3.1.2. Data from repeat dose oral toxicity testing studies shall:
 - II.6.3.3.1.3. Guidance on the design of repeat dose (90-day) studies is...
 - II.6.3.3.1.4. The absence of repeat dose (90-day) oral toxicity studies in...
 - II.6.3.3.2. Repeat-dose (chronic) toxicity testing
 - II.6.3.3.2.1. Chronic toxicity testing shall be conducted in at least one...
 - II.6.3.3.2.2. The data from chronic oral toxicity testing studies shall allow:...
 - II.6.3.3.2.3. Guidance on the design of repeat dose (chronic) studies is...
 - II.6.3.3.2.4. If a repeat dose (chronic) oral toxicity study is not...
 - II.6.3.4. Tolerance in target species, if available

- II.6.3.4. Data on tolerance in target species shall not be required...
- II.6.3.4. ~~2~~ If available, data on tolerance in target species may contribute...
- II.6.3.5. Reproductive toxicity, including developmental toxicity
 - II.6.3.5. Study of the effects on reproduction
 - II.6.3.5. ~~1~~ General reproductive toxicity testing shall be conducted in at least...
 - II.6.3.5. ~~2~~ Tests for effects on reproduction shall aim to identify and...
 - II.6.3.5. ~~3~~ Tests shall identify potential effects on male and female reproductive...
 - II.6.3.5. ~~4~~ If evidence suggests the occurrence of effects on development of...
 - II.6.3.5. ~~5~~ The data shall allow the establishment of a NO(A)EL or...
 - II.6.3.5. ~~6~~ Guidance on the design of reproduction toxicity testing studies is...
 - II.6.3.5. ~~7~~ If a reproduction toxicity study is not provided, its absence...
 - II.6.3.5. Study of developmental toxicity
 - II.6.3.5. ~~1~~ The aim of developmental toxicity studies shall be to detect...
 - II.6.3.5. ~~2~~ If clear evidence of teratogenicity is seen in the rat,...
 - II.6.3.5. ~~3~~ Guidance on the approach towards developmental toxicity testing is described...
 - II.6.3.5. ~~4~~ Studies shall use the oral route of administration.
 - II.6.3.5. ~~5~~ The data shall allow the establishment of a NO(A)EL or...
 - II.6.3.5. ~~6~~ If a developmental toxicity study is not provided, its absence...
- II.6.3.6. Genotoxicity
 - II.6.3.6. In most cases the substance to be tested shall be...
 - II.6.3.6. ~~2~~ ICH GL23: Studies to evaluate the safety of residues of...
 - II.6.3.6. ~~3~~ Results of genotoxicity tests shall be used to evaluate whether...
 - II.6.3.6. ~~4~~ Exposure to certain genotoxic substances is known to be associated...
 - II.6.3.6. ~~5~~ The deliberate use of genotoxic substances that interact directly with...
 - II.6.3.6. ~~6~~ The results from the genotoxicity tests shall contribute to the...
 - II.6.3.6. ~~7~~ A substance that directly induces clearly positive findings in genotoxicity...
 - II.6.3.6. ~~8~~ In the absence of data to demonstrate that observed genotoxicity...
 - II.6.3.6. ~~9~~ Clearly negative results from a standard battery of genotoxicity tests...
 - II.6.3.6. ~~10~~ If unequivocal results are seen in genotoxicity tests, the need...

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- II.6.3.6. ~~I~~ In general the genotoxicity of major metabolites shall be considered...
 - II.6.3.6. ~~I~~ In principle, identification of minor metabolites shall not be required....
 - II.6.3.6. ~~M~~ Minor metabolites are those present at levels below 100 µg/kg...
 - II.6.3.6. ~~I~~ If the structure of a minor metabolite is known or...
 - II.6.3.6. ~~S~~ Similarly, if there is a concern that a minor metabolite...
 - II.6.3.6. ~~F~~ For any of these substances (potentially genotoxic minor metabolites produced...
 - II.6.3.6. ~~I~~ If more than one minor metabolite is DNA reactive, in...
 - II.6.3.6. ~~S~~ Substances and metabolites that may cause cancer by mechanisms other...
 - II.6.3.7. Carcinogenicity
 - II.6.3.7. Criteria for the selection of substances for carcinogenicity testing
 - II.6.3.7. ~~M~~ MICH GL28: Studies to evaluate the safety of residues of...
 - II.6.3.7. ~~I~~ In those cases where carcinogenicity testing is deemed appropriate, the...
 - II.6.3.7. ~~G~~ Genotoxic carcinogens shall not be accepted for use in food-producing...
 - II.6.3.7. ~~A~~ A substance that induces positive findings in carcinogenicity tests may...
 - II.6.3.7. ~~I~~ If carcinogenicity testing is not undertaken, the absence of such...
 - II.6.4. Other requirements
 - II.6.4.1. General principles
 - II.6.4.1. ~~T~~ The need for safety data addressing other potential effects shall...
 - II.6.4.1. ~~F~~ Factors to be taken into account when considering the need...
 - II.6.4.2. Special studies (e.g. immunotoxicity, neurotoxicity)
 - II.6.4.2. Immunotoxicity
 - II.6.4.2. ~~I~~ If relevant effects are seen in repeated dose or other...
 - II.6.4.2. ~~F~~ For certain classes of substance (such as beta lactam antibiotics)...
 - II.6.4.2. ~~D~~ Details shall be provided of all immunological studies performed with...
 - II.6.4.2. ~~D~~ Data obtained from such studies shall be taken into account...
 - II.6.4.2. Neurotoxicity, developmental neurotoxicity and delayed neurotoxicity
 - II.6.4.2. ~~N~~ Neurotoxicity testing shall be required where repeated dose studies indicate...
 - II.6.4.2. ~~S~~ Substances that have been shown in other toxicological assays to...
 - II.6.4.2. ~~N~~ Neurotoxicity testing shall be performed using the oral route and...

- II.6.4.2. ~~2.4.1~~ Although OECD Test Guideline 424 does not specifically address effects...
 - II.6.4.2. ~~2.4.2~~ If a substance has been shown to cause neuropathology or...
 - II.6.4.2. ~~2.4.3~~ Organophosphates shall be tested for delayed neurotoxicity in a hen...
 - II.6.4.2. ~~2.4.4~~ The neurotoxicity studies shall allow the establishment of NO(A)ELs or...
 - II.6.4.3. Microbiological properties of residues
 - II.6.4.3. ~~3.1~~ Potential effects on the human gut flora
 - II.6.4.3. ~~3.1.1~~ For substances with antimicrobial activity, antimicrobial effects on the human...
 - II.6.4.3. ~~3.1.2~~ The data shall be used to derive a microbiological ADI....
 - II.6.4.3. ~~3.1.3~~ The risks that result from residues shall be clearly distinguished...
 - II.6.4.3. ~~3.1.4~~ As described in the VICH GL36, the following two endpoints...
 - II.6.4.3. ~~3.1.5~~ Any departures from the established guidance shall be justified and...
 - II.6.4.3. ~~3.1.6~~ If no testing for effects on the human intestinal flora...
 - II.6.4.4. Observations in humans
 - II.6.4.4. ~~4.1~~ Any available data on health effects seen in humans following...
 - II.6.4.4. ~~4.2~~ The data related to exposure of humans may provide valuable...
- II.6.5. Findings of other EU or international scientific bodies
 - II.6.5.1. If relevant safety evaluations of the substance have been undertaken...
- II.6.6. Determination of an ADI or alternative limit
 - II.6.6.1. Determination of an ADI
 - II.6.6.1. ~~1.1~~ Derivation of the toxicological ADI
 - II.6.6.1. ~~1.1.1~~ The toxicological ADI shall be derived by dividing the selected...
 - II.6.6.1. ~~1.1.2~~ The formula used to determine the toxicological ADI shall be...
 - II.6.6.1. ~~1.1.3~~ The choice of the NO(A)EL or BMDL and the uncertainty...
 - II.6.6.1. ~~1.1.4~~ Unless otherwise justified, the toxicological ADI shall be derived from...
 - II.6.6.1. ~~1.1.5~~ If using the benchmark dose ('BMD') approach, the BMDL shall...
 - II.6.6.1. ~~1.1.6~~ In selecting the default values for the magnitude of the...
 - II.6.6.1. ~~1.1.7~~ In relation to uncertainty factors, the default assumption is that...
 - II.6.6.1. ~~1.1.8~~ Where the results of animal studies indicate teratogenic effects at...
 - II.6.6.1. ~~1.1.9~~ It may occur that the most sensitive endpoint is observed...
 - II.6.6.1. ~~1.1.10~~ The choice of uncertainty factors for use in deriving the...

- II.6.6.1. ~~Where the ADI is to be set on the basis...~~
- II.6.6.1. ~~The~~ refinement of the standard approach for selecting uncertainty factors...
- II.6.6.1. ~~Further~~ refinement of the intra-species and inter-species tenfold uncertainty factors...
- II.6.6.1. ~~For~~ the multiplication of uncertainty factors the use of probabilistic...
- II.6.6.1. ~~The~~ use of these and other approaches for the refinement...
- II.6.6.1. ~~Having~~ regard to the previous considerations, the uncertainty factor used...
- II.6.6.1. ~~Derivation of the pharmacological ADI~~
- II.6.6.1. ~~Pharmacological~~ ADIs shall not be derived for all pharmacologically active...
- II.6.6.1. ~~Guidance~~ on the need for a pharmacological ADI as provided...
- II.6.6.1. ~~Where~~ a pharmacological ADI is needed, the approach for its...
- II.6.6.1. ~~Derivation of a microbiological ADI~~
- II.6.6.1. ~~As~~ described in Section II.6.4.3 microbiological ADIs shall be derived...
- II.6.6.1. ~~The overall ADI~~
- II.6.6.1. ~~Substances with non-threshold effects~~
- II.6.6.2. Alternatives to the ADI
- II.6.6.2. Substances for which recommended dietary intake levels have been established...
- II.6.6.2. ~~For~~ most minerals and trace elements there is a natural...
- II.6.6.2. ~~The~~ ADI approach is not appropriate for use in the...
- II.6.6.2. ~~The~~ approach may be appropriate for minerals, elements, vitamins and...
- II.6.6.2. ~~Substances to which consumers are exposed via food or other...~~
- II.6.6.2. ~~When~~ consumer exposure to residues of the active substance in...
- II.6.6.2. ~~The~~ chemical make-up of herbal/vegetable based products (including extracts) is...
- II.6.6.2. ~~When~~ using this approach it is important to exclude any...
- II.6.6.2. ~~Endogenous pharmacologically active substances~~
- II.6.6.2. ~~If~~ the pharmacologically active substance is identical to an endogenously...
- II.6.6.2. ~~Human~~ exposure to such substances may be expected to come...
- II.6.6.2. ~~Consumer~~ exposure to residues may be best estimated by comparing...
- II.6.6.2. ~~This~~ approach may be appropriate for hormones and other endogenously...
- II.6.6.2. ~~Substances that lack bioavailability~~
- II.6.6.2. ~~For~~ substances that are not absorbed following oral ingestion, systemic...

III. RESIDUE FILE

- III.1. In general a full residue data package shall be required....
- III.2. Detailed and critical summary
 - III.2.1. A detailed and critical summary of the residues file shall...
 - III.2.2. The detailed and critical summary shall:
 - III.2.3. Annexes to the detailed and critical summary shall include:
- III.3. Metabolism and residue kinetics in the target species
 - III.3.1. Metabolism and residues data shall be required to characterise residues...
 - III.3.2. The data shall be provided in the form of a...
 - III.3.3. The test material shall contain the substance of concern in...
 - III.3.4. Guidance provided in VICH GL46: Studies to evaluate the metabolism...
 - III.3.5. Guidance provided in VICH GL49: Studies to evaluate the metabolism...
 - III.3.6. Specific guidance relating to residue studies to be undertaken for...
 - III.3.7. The total residues study (usually performed with radiolabelled drug) shall...
 - III.3.8. A suitable marker residue shall be identified. The marker residue...
 - III.3.9. The ratio of marker to total residues describes the relationship...
 - III.3.10. By monitoring the depletion of total residues in the edible...
 - III.3.11. Information from the metabolism study shall also allow comparison of...
 - III.3.12. Any departures from established guidance shall be justified and the...
- III.4. Monitoring and exposure data, if relevant
 - III.4.1. Monitoring or exposure data of the pharmacologically active substance shall...
- III.5. Residue analytical method
 - III.5.1. A validation report of the analytical method used for quantification...
 - III.5.2. Analytical methods shall be provided at least for those food...
 - III.5.3. The availability of standards shall be confirmed and contact details...
 - III.5.4. Any departures from the requirements above shall be justified and...
 - III.5.5. The analytical method shall be evaluated for compliance with VICH...
 - III.5.6. Following the appropriate authority's opinion, the validation data may be...
- III.6. Potential effects on the microorganisms used for industrial food processing...
 - III.6.1. The residues evaluation shall include an assessment of the potential...
 - III.6.2. The data shall be used to establish a residue concentration...
 - III.6.3. The studies to be performed shall follow the appropriate authority's...
 - III.6.4. Any departures from the established guidance shall be justified and...
 - III.6.5. If no testing of microorganisms used for industrial food processing...
- III.7. Findings of other EU or international scientific bodies
 - III.7.1. If relevant residues evaluations of the substance have been undertaken...

ANNEX II

Methodological principles for the risk management recommendations referred to in Article 7 of Regulation (EC) No 470/2009

I. ELABORATION OF MRLs

- I.1. Derivation of numerical MRLs

- I.1.1. Where it is considered appropriate in accordance with this Regulation...
 - I.1.2. When determining the MRLs, consideration shall be given to the...
 - I.1.3. In deriving MRLs it shall be assumed that the consumer...
 - I.1.4. Using the residue depletion data, the total residue burden in...
 - I.1.5. Once MRL levels have been derived, the Theoretical Maximum Daily...
 - I.2. The 'No MRL required' classification
 - I.2.1. A 'No MRL required' classification may be recommended in those...
 - I.2.2. Substances may be regarded as candidates for a 'No MRL'...
 - I.2.3. In some cases a 'No MRL required' recommendation may incorporate...
- II. AVAILABILITY OF ALTERNATIVE MEDICINES AND OTHER LEGITIMATE FACTORS
- II.1. Availability of alternative medicines
 - II.2. Technological aspects of food and feed productions
 - II.2.1. Where relevant, consideration shall be given to the possibility that...
 - II.2.2. Information on testing that shall be considered in order to...
 - II.2.3. The recommended MRLs shall be set at levels that ensure...
 - II.3. Feasibility of controls
 - II.3.1. For some substances, for which setting numerical MRLs is not...
 - II.3.2. In cases where the time taken for residues to deplete...
 - II.4. Conditions of use and application of the substances in veterinary...
 - II.4.1. For substances proposed for use in species that produce milk or...
 - II.4.2. If appropriate, consideration shall be given to recommending a restriction...
 - II.4.3. If establishment of MRLs may increase the likelihood of misuse...
 - II.4.4. Other factors may be considered on a case-by-case basis where...
 - II.5. Need for an unused portion of the ADI
 - II.5.1. Since it is not possible to predict, with certainty, the...
 - II.5.2. MRL applications usually focus on tissues, however, potential future uses...
 - II.5.3. When considering the need to maintain an unused portion of...
 - II.6. Exposure from other sources (combined exposure to dual-use substances)
 - II.6.1. In order to ensure that all sources of consumer exposure...
 - II.6.2. In the case of substances also used as plant protection...
 - II.6.3. Where the existing pesticide product authorisation allows and sufficient data...
 - II.6.4. As the methodology used in establishing MRLs for edible tissues...
 - II.6.5. For dual-use substances used as biocides in animal husbandry, the...
 - II.6.6. With regard to feed additives, consultation with the European Union...
 - II.7. Injection site residues
 - II.7.1. The muscle MRL shall be set at a level for...
 - II.7.2. For those injectable substances for which depletion of injection site...
 - II.7.3. The ISRRV shall not be published in the Annex to...
- III. CONSIDERATIONS ON POSSIBLE EXTRAPOLATION OF MRLs
- III.1. The extrapolation of MRLs shall be considered in line with...
 - III.2. Data that may be useful in relation to the extrapolation...

Changes to legislation: There are currently no known outstanding effects for the Commission Regulation (EU) 2018/782. (See end of Document for details)

(1) [OJ L 152, 16.6.2009, p. 11.](#)

Changes to legislation:

There are currently no known outstanding effects for the Commission Regulation (EU) 2018/782.