Guidance for the derivation of environmental risk limits

Data collection, evaluation and selection

version 2.0

Colophon

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1.0	2015	
2.0	2025	version history added complete update, removing obsolete parts

Contents

1 Introduction

1.1 Notes to this version

The previous version of this guidance was published in 2015, building on an RIVM report from 2007 [1]. In 2018, the European technical guidance for derivation of environmental quality standards (EQS) under the Water Framework Directive [1] has been revised, and now includes a larger part of the former national methodology. Since RIVM uses the WFD-guidance for derivation of aquatic ERLs, the present document was updated, removing parts that are now sufficiently covered in the WFD-guidance and/or other parts of this national guidance. Some sections from the WFD guidance [2] and the former 2007-guidance that are relevant for other compartment are maintained.

1.2 Scope and structure of this document

The present document deals with the first steps of risk limit derivation: the collection and evaluation of data, which is of crucial importance to ERL derivation. This chapter gives general guidance on collection, evaluation and selection of data, focusing on aspects that are relevant for all compartments, including the presentation of data. The following aspects are addressed:

- data collection and quality assessment
- identity and use (Section 3),
- physico-chemical properties, fate and behaviour (Section 4),
- ecotoxicity (Section 5),
- human-toxicological threshold limits (Section 6)

2 General guidance on data collection and quality assessment

2.1 Collection of data

For most physico-chemical properties, database endpoints may be sufficient for ERL derivation since they are primarily needed to gain insight into the environmental behaviour of a compound. These compound properties are used as background information to enable interpretation of ecotoxicity tests. In cases where the data are more critical, such as input in model calculations like equilibrium partitioning and the calculation of soil standards based on indirect exposure of humans, a critical review may be needed.

The main environmental fate parameters needed are partitioning constants and information on physical, chemical and biological degradation, of which both database values and values collected from original sources are used. If an ERL for soil or sediment has to be derived by means of equilibrium partitioning, information on the sorption characteristics is of crucial importance and should be collected. More detail on collection methods for distribution constants is given in sections 4.2.5 and 4.2.6. Information on degradation of the substance considered is generally not used quantitatively in ERL derivation. However, this information is crucial to understand the behaviour of the substance in toxicity tests and in the environment. Data on e.g. hydrolysis, photolysis and biodegradation are collected and tabulated, but the underlying original sources are generally not evaluated, unless this becomes crucial for the derivation of the risk limit under consideration.

The collection of ecotoxicity data consists of multiple steps. The screening procedure is worked out in detail in section 5.1. First, data are gathered from secondary sources such as databases, handbooks, evaluation reports prepared in the context of authorisation (e.g., agricultural pesticides, biocides) or risk limit derivations prepared by other countries. The second step is to retrieve the studies underlying these secondary sources and to evaluate these. Thirdly, primary data are retrieved from the open literature. It is noted that with respect to ecotoxicity data, a full literature search is carried out in most cases. For human-toxicological data, data collection is only needed if an established health based guidance value is absent or if re-evaluation of an old value is needed. The collection procedure for ecotoxicity data is described in more detail in section 5.1.

2.2 Reliability and usefulness

All data have to be evaluated with respect to reliability and to that end, the original data source (publication, study report) should be retrieved whenever possible. In principle, this also holds for studies that already have been accepted for use in another regulatory context. According to the WFD guidance, data that have already been subjected to data quality assurance and peer review and are published in risk assessment reports under other legal frameworks, may be used, based on summaries in those reports. It should be noted that these summaries

should be robust, i.e., contain enough information and detail to enable the assessor to judge whether the earlier study evaluation has adequately addressed reliability and usefulness with respect to use in ERL derivation. This should be done with care, since not all studies that have been accepted earlier meet the quality criteria that are applied nowadays. For instance, analytical verification of test concentrations was not common practice in the past and may be critical in case of fast dissipating or hydrophobic substances.

Reliability of a study pertains to the intrinsic, scientific quality of an individual study, and is determined by the set-up, performance and evaluation of the experiment, and the reporting . A study may be properly reported, but considered less or not reliable because of an inadequate set-up (e.g., too few replicates) or performance (e.g., high control mortality). Sometimes, a study that was seemingly carried out in a scientifically sound way, cannot be properly evaluated because the description is so concise that the experimental set-up cannot be judged adequately (e.g. the study or its methods reported as a reference to another report), or if various items that are considered important for interpretation of the test results cannot be checked (e.g. temperature data are not given). Reliability indices (Ri) are used to designate the reliability of a test or study, with Ri 1, 2, or 3 reflecting reliable, less reliable, and unreliable test results, respectively. A fourth category, Ri 4, is added for references which due to limited or inadequate reporting cannot be evaluated. The reliability assessment is historically performed applying the criteria of Klimisch et al. [3]):

1. reliable without restrictions: 'studies or data...generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline... or in which all parameters described are closely related/comparable to a guideline method.'
2. reliable with restrictions: 'studies or data... (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.'
3. not reliable: 'studies or data...in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.'

4. not assignable: ‘studies or data....which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).’

Reliability checklists for specific tests within the context of pesticide evaluation have been published by RIVM [4-7]. Meanwhile, additional assessment schemes and checklists have been developed for aquatic ecotoxicity studies, such as the CRED-methodology [8,9], offering the ability to further assess reliability and relevance of aquatic ecotoxicity data in a systematic way. Additional guidance on reliability assessment can be found in the endpoint specific guidance of REACH [10-12].

In general, when a test has fundamental shortcomings, it should be classified as not reliable (Ri 3). This applies e.g. to situations where the identity of the substance is improperly characterised or reported [7], ecotoxicity tests that are incubated too long (e.g. for algae) or too wet (for soil), or in which control mortality was higher than allowed according to the relevant guidelines. Studies performed and reported according to accepted international guidelines are generally reliable when the requirements of the protocols are met, although these studies should also be carefully evaluated. Hence, following an accepted protocol is not a prerequisite for being considered reliable (Ri 1 or 2), nor is the applicability of a formal quality assurance scheme, such as Good Laboratory Practice. The reported description of a study, should provide all information necessary to assess its quality. If a test result is not (properly) reported, but can be (re)calculated from the data presented by the author(s), the result is also used. This also applies to results presented in graphs that might be converted back into raw data. If more information from comparable studies and organisms is available, this can be involved to judge plausibility of the respective studies, but this is not a part of intrinsic reliability.

Good quality tests may be considered not useful or not relevant for ERL derivation. This is the case when a parameter is derived under conditions that are not considered relevant for the field situation, for instance when a DT50 for hydrolysis relates to a pH of 10 and 50°C. Tests that are not relevant for the purpose of ERL derivation may still contain information that is useful as circumstantial evidence. An example is an ecotoxicity experiment that is carried out in a medium that is not the natural habitat of the tested species. Results of a terrestrial plant test that is carried out in water, cannot be used as a basis for ERL derivation. These tests may still be valid and reported with Ri 1 or 2, but it should be clearly indicated that the endpoint is not considered relevant for ERL derivation. However, such a test may provide information that is useful, e.g. to show that macrophytes are likely not sensitive. Other examples of studies that contain useful ecotoxicity information but cannot be used directly for derivation of ERLs, are a NOEC value from a short term test, or a value higher than the highest tested concentration or lower than lowest tested concentration. The judgement of relevance is thus highly dependent on the context of ERL derivation. Generic considerations on relevance assessment are discussed by [9], specific guidance is given in the respective chapters (see sections 5.2.4 and 5.2.9).

3 Substance identity and use

3.1 Identification

For a proper identification of the chemical under consideration, information is presented on names, registry numbers and formulas of the compound. The required information may be presented in a table format which is also included in the ERL report (Table 1).

Table 1 Identification of substance [name]. Example of the table format used for the identification of the substance under evaluation.

Parameter	**Value**
Chemical name	indicate if this is IUPAC or CAS name or otherwise
Common/trivial/other name	trade names, product names
CAS number	
EC number	
Molecular formula	CxHyOz
Molecular mass	
Structural formula	
SMILES code	

The information may be collected from various sources including public data from the ECHA website, PubChem, the US EPA Ecotox database [13] and information from EPI Suite™ [14]. General handbooks like Mackay et al. [15] can be consulted. For pesticides and biocides, reference is made to the assessment reports prepared in the context of European active substance approval, available via EFSA and ECHA, respectively. If not available from these datasources, SMILES code can be generated using chemical drawing software, e.g., ChemSketch [16].

➔ location in WFD guidance: Appendix A1.1.

3.2 Information on use

Next to information on identity, it is advised to collect information on the use of the compound and the main emission sources, e.g., industrial categories or agricultural application. Information on the function (herbicide, fungicide, insecticide, disinfectant, biocide, antifouling, veterinary pharmaceutical, antibiotic, human pharmaceutical, anti-cancer drug, cardiovascular drug, flame retardant, etc.) and mode of action is also presented. This information may be added to the table, or presented in a separate section when given in more detail.

Various sources are used, starting with the risk assessment reports that are made publicly available in the respective frameworks, such as EU RARs or the REACH dossier data (dossiers are accessible via https://echa.europa.eu/information-on-chemicals, see section on Manufacture, Use and Exposure information). For plant protection products or biocides, the respective assessment reports should be consulted, which are available via EFSA and ECHA, respectively. For human pharmaceuticals the European Public Assessment Reports (EPAR)

published by EMA are a relevant source (https://www.ema.europa.eu/en/medicines). Apart from these sources, handbooks like e.g., Pesticide Manual can be consulted. Within the context of resistance management, industry parties provide information on the mode of action of plant protection products at the websites of the respective Resistance Action Committees for fungicides (FRAC), herbicides (HRAC) and insecticides (IRAC).

4 Physico-chemical properties, fate and behaviour

4.1 Data collection

The following physical and chemical parameters and data on behaviour are collected for the molecule of interest:

- melting point: T_m, (°C);
- boiling point: T_b, (°C);
- vapour pressure: P_v (Pa), experimentally determined values for melting point and boiling point can be useful for estimation of the vapour pressure;
- Henry's law constant: H ($Pa.m^3/mol$).
- water solubility: S_w (mg/L), an experimentally determined value for melting point can be useful for the estimation of the solubility from log K_{ow} ;
- dissociation constant: pK_a (-);
- *n*-octanol/water partition coefficient: K_{ow} (-);
- soil/sediment water partition coefficient: K_p, (L/kg_{dw}).
    - For organic substances, the partition coefficient normalised to organic carbon is preferred: K_{oc} (L/kg_{oc}).
    - For metals, field based partition coefficients (K_p) are preferred.
- additional information on environmental fate, such as dissipation half-life times in water, soil and sediment due to e.g. hydrolysis, photolysis and/or biodegradation.

➔ Location in WFD guidance: Appendix A1.2
➔ REACH guidance document R7.a [12]

Properties that are associated with potential high disappearance from the test solutions (e.g., high vapour pressure, low solubility, high K_{ow}, fast hydrolysis) give an indication that special care should be taken to maintain test concentrations during the experiment and/or that test endpoints should be based on measured concentrations only. For the derivation of ERLs for soil or sediment, an additional evaluation of sorption characteristics may be needed in case an ERL has to be derived by means of equilibrium partitioning.

For plant protection products and biocides, the assessment reports prepared in the context of European substance approval procedures are used as the primary source of information (see section 5.1). Log K_{ow} should additionally be obtained using the BioLoom software (former ClogP) [17]. Additional information may be obtained from the OECD QSAR Toolbox [18] and general handbooks such as the Pesticide Manual [19].

For other compounds, log K_{ow} is also derived from BioLoom [17]. Most recommended values from the MacKay-handbook [15] are included in the SRC database that is part of EPI Suite™ [14]. The program does not search online, and thus gives a momentary view of the data sources at the time of release of the present version. For the data on physico-chemical properties, this is not considered as a serious drawback, since major changes in parameters are rare and hence databases for these

properties are generally not frequently updated. REACH dossiers [13] should also be consulted. Care should be taken to verify whether the latter data sources do contain data that have been evaluated. REACH dossiers may contain data that have been evaluated previously in the context of other regulatory frameworks, but reliability indices are designated by the registrant.

4.2 Data evaluation and selection

As noted in section 2.1, database endpoints on physico-chemical parameters are generally considered sufficient as background information for the interpretation of ecotoxicity tests. In case primary data sources such as peer-reviewed literature are collected, these studies are evaluated according to the reliability criteria in section 2.2.

In most cases, the evaluation consists of a general assessment of database results, e.g., the suitability of the reported methods is evaluated in relationship to the properties of the compound, depending on the available data on the evaluated properties. Lipophilicity is inversely related with water solubility. Hence, if for a compound the reported log K_{ow} and water solubility are both relatively high or both relatively low, the reliability of the data on these properties should be further investigated, e.g., by attempting to retrieve more data or QSAR estimates of both parameters.

The relevant and reliable data may be summarised in an overview table according to the format below (Table 2). If for a given parameter more than one result is available, these are all listed and it is indicated what is the representative value to be used for derivation of ERLs. In the next sections, some parameters are discussed in more detail. Specific guidance is given on the evaluation of experimental data and on estimation methods in case of absence of data, and advice is given on the selection of the appropriate endpoints.

Table 2 Default table structure for reporting physico-chemical and fate parameters.

Properties	**Value**	**Unit**	**Reference**
Melting point		°C	
Boiling point		°C	
Vapour pressure		Pa	
Henry's law constant		$Pa.m^3/mol$	
Water solubility		mg/L	
pK_a (specify reaction[a]1 to which pK_a applies)			
log K_{ow}			
log K_{oc}			
log K_p			
log $K_{p,\ susp}$			
Dissipation half-life (DT50) or degradation half-life [b] (DegT50) for		hours, days	

[1].

Properties	Value	Unit	Reference
hydrolysis/photolysis/biodegradation in water and/or sediment			

a: pK_a values are not informative unless the dissociation reaction to which the value applies is presented. E.g. pK_a for $RN^+H \rightarrow RN| + H^+$
b: DT50 is used for hydrolysis, photolysis and non-microbial removal in biodegradation studies. DegT50 is used when the half-life value is known to represent biodegradation.

4.2.1 *Vapour pressure*

The experimental determination of the vapour pressure of a compound is described in OECD guideline 104 [20]. In this guideline several methods are discussed, each with its own range of applicability. The following table presents information from the guideline, which specifies what method is suitable for which compound.

Table 3 Domain of applicability of different methods for the determination of vapour pressure [20].

Method	Suitable for liquids	Suitable for solids	Recommended range
Dynamic method	low melting	Yes	10^3-10^5 Pa
Static method	yes	Yes	10-10^5 Pa
Isoteniscope	yes	Yes	10^2-10^5 Pa
Effusion method	yes	Yes	10^{-3}-1 Pa
Gas saturation method	yes	Yes	10^{-5}-10^3 Pa
Spinning rotor method	yes	Yes	10^{-4}-0.5 Pa

In the dynamic method (Cottrell's method), the boiling point of a compound is determined at various pressures between about 10^3 and 10^5 Pa. In the static method, the vapour pressure is determined at one specified temperature by means of a manometer (e.g., 25ºC). The isoteniscope method is based on the same principle as the static method, and although it was developed to measure the vapour pressure of certain liquid hydrocarbons it is appropriate for solids as well. The method is usually not suitable for multicomponent systems. In the effusion method the weight loss of the compound is measured. This can be done directly by measuring the mass of the remaining substance or by analysing the volatilised amount by gas chromatography (GC). In the updated OECD guideline 104 [20], isothermal gravimetry is added for the effusion method. The weight loss is then determined at different temperatures and an extrapolation to 20 or 25ºC can be made. The range of vapour pressures that can be determined with this method is 10^{-10} to 1 Pa. The gas saturation method makes use of a column containing a carrier material supporting the substance, through which an inert gas is passed. The concentration of the substance in this carrier gas is then determined, usually by GC. The last method is the spinning rotor method, where the retardation of a spinning ball due to the friction with the gas phase is measured.

In general, the methods that make use of an analysis of the substance, for example by gas chromatography, are less prone to errors due to impurities than the other methods. The OECD guideline does not mention this explicitly. However, degassing of more volatile compounds prior to the determination of the vapour pressure also enhances the

reliability of the determination. The retention time in gas chromatography can be used to estimate the vapour pressure of a compound. Although this is not a direct determination of the vapour pressure, it generally gives rather accurate results and is applicable to substances with a very low vapour pressure. In addition to this, the vapour pressure can be estimated by the programme MPBPwin, which is incorporated in EPI Suite™ [14]. The programme makes use of three estimation methods, which are the Antoine method, the modified Grain method and the Mackay method. All three methods use the boiling point and melting point of the compound for their estimation of the vapour pressure. Both boiling and melting point can be estimated by the programme, but experimental values can also be entered if known. For solids, the result of the modified Grain method is presented as the preferred value, while for liquids this is the mean of the Antoine method and the modified Grain method.

Experimental and estimated values are both reported. If results from different methods deviate significantly from each other, only the methods with a direct analysis of the compound should be used, such as the gas saturation method. Complementary to this, the data from GC retention times may be used if there are not enough reliable data. If no experimental data are available, the estimate from EPI Suite™ as included in the OECD QSAR Toolbox can be used[2].

4.2.2 *Henry coefficient*

No general accepted guideline exists for the determination of the Henry coefficient. However, several methods exist to determine the Henry coefficient experimentally.

In the batch stripping method, gas is bubbled at a known rate through a solution of the compound in water. The Henry coefficient is calculated from the decrease in the aqueous concentration, using the mass balance. The concentration in air is generally not measured. This method works well for fairly volatile compounds with Henry coefficients higher than 2.5 and occasionally down to 0.25 $Pa.m^3/mol$ [21].
One common method, very similar to the batch stripping method, is the gas stripping method in which a gas is bubbled through the aqueous solution and both the aqueous concentration and the gas concentration are determined. The technique was applied to chlorobenzenes, polyaromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs), in a range from 0.018 to 276 $Pa.m^3/mol$ [22].

A method for highly volatile compounds (i.e. higher than 120 $Pa.m^3/mol$) is the Equilibrium Partitioning In Closed Systems (EPICS) method. With this method a known volume of solute in water solution is equilibrated with air in sealed vessels. The headspace air concentrations are measured. The method has a high precision [21]. A number of other headspace analysis techniques that are used, are slightly different from the EPICS method, in some techniques not only the headspace but both phases are analysed [21].

[2] QSAR Toolbox

A method for less volatile compounds is the wetted-wall method. In this method the solute is equilibrated between a thin flowing film of water and a concurrent air flow in a vertical column. Both phases are measured. The method has been applied to pesticides and other less volatile compounds, but no recommended range is given [21]. In the cited handbook, values for PCBs, PAHs, and two pesticides are tabulated using this method. Values for PCBs and PAHs range from 0.91 to 74.3 $Pa.m^3/mol$. One of the pesticides (alachlor) has a much lower Henry coefficient of 8.43×10^{-4} $Pa.m^3/mol$. This is in agreement with the method being suitable for less volatile compounds.

The Henry coefficient is sometimes related to retention times [21]. However, results obtained using this method should be considered as an estimate. Another estimation that is often used for the Henry coefficient is the quotient of vapour pressure and solubility. This method works quite well for substances that have a solubility of less than 1% in water. The Henry coefficient can also be calculated by a bond contribution method as included in EPI Suite™ [14]. These estimated values should be included in the physico-chemical data table.

The validity of values for the Henry coefficient should be considered on a case-by-case basis. When no reliable experimental values are available, the Henry coefficient can be estimated from the quotient of the vapour pressure and the water solubility, provided that reliable values are available for both parameters. If this is not the case, the estimate from EPI Suite can be used [14].

➔ Location in WFD guidance: Appendix A1.2.3.

4.2.3 Water solubility

Two methods for the experimental determination of water solubility are described in OECD guideline 105 [23]. These methods are the flask method (shake-flask) and the column elution method (generator column). The flask method can be used for compounds with a solubility higher than 10 mg/L. Below that value, colloid formation will overestimate the true aqueous solubility and in that case the column elution method should be used, which prevents this phenomenon. Apart from the methods proposed in the OECD guideline, the water solubility of poorly soluble liquid compounds can be accurately determined by means of the slow-stirring method. The reliability of the slow-stirring method applied to liquid substances can be considered equivalent to that of the column elution method. Only few examples are available of the use of this method for the determination of solubility, mostly for hydrocarbons and phthalate esters [24-26]. This method is often used to prepare saturated solutions of hydrocarbon mixtures (oil products) in water (water accommodated fractions or WAF), by which information on the solubility of a mixture is given [27].

Estimates of the water solubility can be made by two different programmes included in EPI Suite [14]. These programmes are WSKOWwin, which estimates the solubility from log K_{ow}, and WATERnt, which is a fragment method for water solubility independent of log K_{ow}. Experimental values for log K_{ow} and melting point can be entered in WSKOWwin if available. Otherwise WSKOWwin will use the default

values (experimental or calculated) from EPI Suite for these parameters. These estimated values should be reported as well in the data tables.

The selected value for water solubility may be calculated from the geometric mean of all valid values for the water solubility. Values below 10 mg/L determined with the shake-flask method should be considered as unreliable. For these poorly soluble compounds, the geometric mean of the generator column and slow-stirring method is used as selected value.

4.2.4 Dissociation constant(s) – pK_a

It should be reported whether the substance under investigation contains groups that dissociate upon dissolution in water. When it is known that a substance is neutral at environmentally pH values (pH range 5 – 10), this is worthwhile information, especially for more complex molecules. For substances that contain dissociating groups, the pK_a values should be collected and preferably a short description is given on how the molecule is charged as a function of pH.
Experimentally determined pK_a values are preferable, but values from handbooks, databases or computation software are tabulated as well. For the latter, e.g. Marvin Sketch [28] could be used.
For both acidic (proton donating) groups and basic (proton accepting) groups, the pK_a value should be reported. In both cases, this is the equilibrium constant for the proton releasing reaction. For bases this is the equilibrium constant for the proton releasing reaction of the conjugated acid. For example:

$C_6H_5\text{-}OH + H_2O \rightarrow C_6H_5\text{-}O^- + H_3O^+$

is the reaction for the dissociation of the weakly acidic phenolic group of phenol. The pK_a of this reaction is 10.0. This means that at pH 12 the molecule will be in its ionised form (1-) for ~99% and at pH 8 the molecule will be in its neutral form for ~99%. Below pH 8 the neutral fraction will only increase further.

$C_6H_5\text{-}NH_3^+ + H_2O \rightarrow C_6H_5\text{-}NH_2 + H_3O^+$

is the reaction for the acidic dissociation of the conjugated acid of aniline. The pK_a of this reaction is 4.6. Note that the pK_b of aniline is 9.6. A pK_a of 4.6 means that at pH 2.6 the molecule is present in its ionised form (1+) for ~99% and at pH 6.6 the molecule is present in its neutral form for ~99%. The neutral form will be even more dominant at increasing pH values.
If there are several dissociating groups in the molecule, clarify which pK_a is valid for which group and reaction. The most acidic pK_a value is given an index of 1: pK_{a1}, the second one an index of 2 (pK_{a2}), etc.

4.2.5 Octanol/water partitioning coefficient K_{ow}

Several methods are available for the experimental determination of log K_{ow}. Three methods are described in OECD guidelines and a fourth method is described in a draft guideline. The first method is the shake-flask method: OECD guideline 107 [29]. This method is applicable to compounds with log K_{ow} values in the range between -2 and 4 (occasionally up to 5), but is impossible to use with surface-active

materials. For these materials, a calculated value (using BioLoom [17]) or an estimate based on individual *n*-octanol solubility and water solubility should be provided, preferably in mutually saturated *n*-octanol and water [30-32].

The second method is the HPLC method. Values of log K_{ow} in the range between 0 and 6 can be estimated using high performance liquid chromatography: OECD guideline 117 [33]. The HPLC method is not applicable to strong acids and bases, metal complexes, surface-active materials or substances which react with the eluent. The HPLC method is less sensitive to the presence of impurities in the test compound than is the shake-flask method. Nevertheless, in some cases impurities can make the interpretation of the results difficult because peak assignment becomes uncertain. For mixtures which give an unresolved band, upper and lower limits of log K_{ow} should be stated.

The slow-stirring method is the third method. It determines the distribution of a compound between *n*-octanol and water directly, with a range of applicability extending beyond that of the shake-flask method: OECD guideline 123 [34]. With this method, log K_{ow} values up to 8.2 can be accurately determined, making it suitable for highly hydrophobic compounds. This method prevents the formation of micro droplets of *n*-octanol in the aqueous phase, which results in an overestimation of the water concentration and, consequently, an underestimation of the log K_{ow} value. For the same reason, the shake-flask method can only be used up to log K_{ow} values of around 4 and definitely not higher than 5.

Another method, not mentioned in OECD guidelines, is the generator-column technique. Although this technique is most frequently used for the determination of water solubility, it is occasionally used for the determination of log K_{ow}. Because the supporting material silica, saturated with *n*-octanol containing the compound, is held in a column, the formation of micro droplets is excluded. For this reason, the results from this technique can be considered equivalent to results obtained with the slow stirring method. In general, good correlation exists between the slow stirring method and the generator column technique, within the experimental error of both methods. However, only a limited number of studies is available that use this technique, primarily for chlorinated biphenyls and dibenzodioxins (e.g. [35-42]).

Before deciding on what procedure to use, a preliminary estimate of log K_{ow} should be obtained from calculations (see the annex to Guideline 117), or where appropriate from the ratio of the solubilities of the test substance in the pure solvents. Still, the HPLC method should be regarded as an estimation method for log K_{ow}, because it does not directly measure the distribution of a compound between octanol and water.

Besides experimental determination, log K_{ow} values can also be calculated with a QSAR programme. The log K_{ow} values calculated with ClogP (BioByte, 2004) and EPI Suite™ [14] should always be presented for comparison. Both programmes are based on a fragment contribution method. The log K_{ow} value that is selected for use in the ERL derivation is preferably the selected experimental value (MlogP) presented by

BioLoom [17]. This value is assigned the highest quality in the underlying MedChem database. Only if this database does not give a selected value or when careful considerations lead to a different selection, the selected log K_{ow} value may be the average value of all reliable log K_{ow} values determined by the shake flask, slow stirring or generator column method. Since log K_{ow} values estimated using the HPLC method are indirect estimates of octanol/water partitioning and are therefore not regarded as most reliable, they should not be used when more reliable data are available. When no or only unreliable experimental data on log K_{ow} are available, the ClogP value of BioLoom [17] is preferred.

4.2.5.1 Ionisable substances

Determination of the partition coefficient of ionisable organic compounds requires extra attention. Based on the collected pK_a values (section 4.2.4) it can be inferred at what pH values the molecule is charged and where it is neutral. Take care that some substances are always charged in solution and that substances may be zwitterions, i.e. they may be charged at several places in the molecule, but their net charge may be zero at given pH values.

A partitioning coefficient of an ionisable molecule at a pH where the molecule is not fully neutral is called a D_{ow} rather than K_{ow}. The K_{ow} is defined as the *n*-octanol:water partitioning coefficient for the fully neutral species. As said, for some molecules this may be a theoretical value as these substances never become neutral in aqueous solution. QSAR determined values of K_{ow} for ionisable substances in principle pertain to the fully neutral form of the molecule, if this form exists. Some QSAR software also enables to calculate either D_{ow} values or lipophilicity-pH profiles, e.g. Marvin Sketch [28]. This is a useful tool if the lipophilicity-pH profile of the compound is complex.

For simple molecules, with few dissociating groups, K_{ow} may be determined by performing the determination of K_{ow} at a pH value where the molecule is fully neutral. A practical approximation of 'fully neutral' is a fraction of at least 99% of non ionisable species in solution, which is reached at ≥ 2 pH units above or below the pK_a value, for molecules with one dissociating group. The outcomes of studies performed in this way may be accepted to reflect the K_{ow}. If the study has been conducted at pH values where the molecule is not fully neutral, the outcome should always be reported as D_{ow}, together with the pH of determination.

D_{ow} determinations of acids and bases with one dissociating group can be easily recalculated to a K_{ow} or to a 'ion corrected D_{ow}'. This calculation is based on the Henderson-Hasselbalch equation and can be found in textbooks. We cite from Schüürmann et al. [43]. For the dissociation of an acid ($AH \rightarrow A^- + H^+$) the fraction of non dissociated acid is:

$$f_{\text{u, acid}} = \frac{1}{1+10^{\text{pH}-\text{p}K_a}} \quad (1)$$

Further:

$$D_{\text{ow}} = f_{\text{u}} \cdot K_{\text{ow}}, \quad (2)$$

and equations 1 and 2 combine to:

$$K_{ow} = D_{ow} \cdot (1 + 10^{(pH - pK_a)}) \quad (3)$$

And for the dissociation of a base (BH+ $\rightarrow$ B + H+):

$$K_{ow} = D_{ow} \cdot (1 + 10^{(pK_a - pH)}) \quad (4)$$

If it is possible to derive a value for K_{ow} as an ion corrected value of the D_{ow} available, this value should be presented in the section on physico-chemical properties, with the note that it concerns a ion corrected log D_{ow}.

A revised draft OECD guideline was published [44] describing a potentiometric method to determine the pH-lipophilicity profile of a substance. This method is also described in the scientific literature, e.g. in Avdeef [45] and Takács-Novák and Avdeef [46]. The method is also applicable to multiprotic substances, i.e. substances with more than one proton donating group. Results for log K_{ow} obtained using this method may be valid, provided that the method used is well reported and can be evaluated.

In the interpretation of the tabulated results, K_{ow} should be used as main descriptor of the potential for bioaccumulation. For substances that are not neutral within the environmentally relevant pH range (5-9) and consequently have D_{ow} values in that range that are lower than their K_{ow}, these D_{ow} values should not be automatically be used to conclude that 'no bioaccumulation potential' exists, if the value is below the appropriate trigger value. The bioaccumulation potential of the ionised part of the molecule is generally expected to be lower than that of the neutral species, but the extent to which this is true is generally not known.

4.2.6 Partitioning coefficients for organic compounds and metals

For a glossary of partitioning theory, see Annex 1.

4.2.6.1 Organic compounds - organic carbon normalised partitioning coefficients

The organic carbon normalised partition coefficient (K_{oc}) is calculated or directly retrieved from literature. The soil or sediment type that is used to determine the partition coefficients (e.g. sediment, loamy sand, suspended matter) is reported in the table. The organic carbon content is also reported. The method to determine the K_{oc} most accurately is OECD guideline 106 [47]. All K_{oc} values that are determined with a method similar to this guideline method can be regarded to be reliable and are preferably used, if well performed and described. The REACH guidance also allows K_{oc} values to be derived using the HPLC method according to OECD guideline 121 [48]. The HPLC method is no direct determination of the K_{oc} but an estimate based on another property (retention in HPLC). Other options are soil column studies according to OECD guideline 312 [49], or field studies or simulation studies. Expert judgement is required for evaluation and interpretation of the results of these latter studies [50]. If reliable, the results can be used but will most often be considered as additional information.

K_{oc} may also be estimated. More information can be found in the REACH guidance [12]. If no experimental values are available, estimated from

the EPI suite estimation routine KOCwin may be used, which employs a calculation method based on log K_{ow} and molecular connectivity indices (MCI). In addition, the QSAR models presented in the former Technical Guidance Document (TGD) [51] should be used. These models originate from Sabjlić et al. [52] and are based on the relationship between K_{ow} and K_{oc}. Table 5 gives the QSAR models, the domain and statistics of the models. In principle, the appropriate QSAR should be chosen based on this table. For many compounds with polar groups attached, a separate QSAR is available for that particular chemical class. In general, these QSARs do not deviate very much from the QSARs for larger subsets of chemical classes. However, if there is doubt about which QSAR to use, for example, due to the presence of more than one functional group, it is often most convenient to use the more general QSARs, in particular the QSAR for non-hydrophobic chemicals. This QSAR, together with the QSAR for predominantly hydrophobic compounds provides a reasonable estimate of the K_{oc} for most compounds.

For the selection of the K_{oc} value, experimentally determined values according to standardised tests (e.g. OECD guideline 106;[47]) or from other studies published in scientific literature are preferred. K_{oc} values determined by the HPLC method (OECD guideline 121; [48]) should be considered as estimates of the real K_{oc} values and consequently, these values are not used as experimental values. The geometric mean of the valid experimental K_{oc} values is calculated. K_{oc} values estimated with EPI Suite™ [14] and other estimates may be presented for comparison. In case experimental K_{oc} values vary widely and no value for K_{oc} can be considered as the most reliable value, consider to calculate the geometric mean of all valid K_{oc} values, including both EPI suite KOCwin estimates and appropriate QSAR estimates. This geometric mean K_{oc} can then be used as the selected value in ERL derivations [53].

4.2.6.2 Metals

Adsorption of metals to the solid fraction of soil, sediment or particulate (suspended) matter depends on many variables such as cation exchange capacity, organic matter content and clay content, pH, redox potential, etc. In contrast to organic compounds, there is no estimation method to predict metal-solids partitioning in environmental compartments from compound properties. Thus, partition coefficients for metals have to be determined in and retrieved from experimental studies.

The K_p values are collected from all valid studies reporting metal partition coefficients. Relevant studies are those that report partitioning or distribution coefficients, represented by K_p or $K_{d,}$ respectively for sediment, soil or suspended matter determined in field samples. See Appendix 2 for an explanation on terminology of partitioning coefficients.

Batch adsorption studies, performed in the laboratory, are a second type of potentially relevant studies. A few references that are of interest are Sauvé et al. [54] and Bockting et al. [55], although values of the latter have been criticised [56]. Due to the heterogeneity of adsorbents as well as conditions encountered in various compartments, K_p values for metals usually show a high variation. Since normalisation is generally not feasible, selection of the K_p value(s) to be used in equilibrium

partitioning calculations needs careful consideration. If experimental data on K_p for metals are lacking, the data gap should be reported.

When collecting suspended matter:water partitioning coefficients from field studies, it is important to establish for each study if the water fraction was filtered before the metal concentration was determined in the aqueous phase. If the water phase was not filtered before metal analysis, the water concentration represents a 'total concentration'. The resulting partition coefficient is then a $K_{p,\ susp\text{-}water}$ for the 'total water concentration'. If the water sample is filtered (usually using a 0.45 µm filter) before analysis, the metal concentration represents a dissolved concentration. The assessor should report for each K_p value, whether it concerns a K_p based on total or dissolved concentrations. Since ERLs are generally expressed as dissolved concentrations, only K_p values based on dissolved concentration measurements can be used to convert ERLs to a total concentration.

4.2.7 Data on removal processes

Insight into the behaviour of the test substance with respect to potential removal processes during ecotoxicity testing is highly relevant in assessing the validity of these tests. We discern physical/chemical and biological removal processes.

4.2.7.1 Physical and chemical removal

Data on vapour pressure (section 4.2.1) and Henry coefficient (section 4.2.2) have been collected and indicate whether the substance volatilises easily from aqueous solution or from soil (N.B. terrestrial toxicity studies). If the data collected indicate that the substance volatilises easily, ecotoxicity studies should be checked on appropriate analysis of the test substance and/or appropriate test set up to minimise evaporation.

Data on solubility/lipophilicity (section 4.2.3, 4.2.5) have been collected and indicate low soluble/lipophilic substances, that may disappear rapidly from solution due to sorption processes to matrix, biota and test vessel material. For such substances, dissolving the substance and maintenance of exposure concentration may become challenging. Care should be taken that appropriate sampling and analysis is employed, with a method and limit of detection allowing for accurate determination of the actual exposure concentrations. In addition the test set up may be need to be adapted, e.g. using a generator column or renewal or flow-through systems to enable appropriate testing of the substance.

Photodegradation data may be collected from peer reviewed assessment reports that are available from registration frameworks (PPP, biocides, REACH, OECD, etc.), databases or handbooks that contain these data. Preferred data are those that express half-life values under realistic conditions. If available, the light source used to obtain the results should be tabulated as well. If photodegradation is relevant as a removal process, the possibility of degradation in toxicity tests should be evaluated.

Hydrolysis. Data may be collected from peer reviewed assessment reports that are available from registration frameworks (PPP, biocides, REACH, OECD, etc.), databases or handbooks that contain these data.

The temperature and pH at which the hydrolysis rate is determined should be tabulated as well. If hydrolysis is relevant at ambient temperature and environmentally relevant pH levels, this should addressed when interpreting the ecotoxicity tests. When interpreting hydrolysis tests for lipophilic substances, care should be taken that disappearance of the substance is not automatically interpreted as hydrolysis. A mass balance determination in the OECD 111 [58] hydrolysis test is optional, especially when non-radiolabelled test substances are used. If a mass balance (at all sampling points during the test) has not been established, disappearance of the substance, measured only by a reduction of the analyte concentration in water may be caused by adsorption to test vessel material or volatilization.

4.2.7.2 Biological removal

Half-life values for biodegradation of the test substance in water, sediment or soil are collected. It is generally sufficient to tabulating data found in other data sources. If a general picture on the biodegradability of the substance emerges, this is normally sufficient to aid in evaluation of ecotoxicity studies. In specific cases, biodegradation may be a crucial parameter and in depth analysis of the data and thus underlying studies may be warranted. This approach is considered an exception rather than the rule and is not the standard approach.

5 Ecotoxicity data

5.1 Data collection

As indicated in section 2.1, the collection of ecotoxicity data consists of multiple steps. If the ERL is being updated, the former derivation report is taken as a starting point. For all other ERLs, first, data are gathered from secondary sources (databases, evaluation reports or risk limit derivations prepared by other countries). Next, the underlying studies are collected and evaluated and additional primary data are retrieved from open literature and other public sources. A thorough evaluation of all relevant studies is needed, using the appropriate evaluation methodology (see below). Due to data protection, it is often hard to get access to original study reports that are prepared by industry parties for registration purposes. An option that should always be considered is to explicitly invite stakeholders to submit their data for ERL derivation.

As an alternative option, we also accept summaries prepared for authorisation of compounds under various (European) legal frameworks, provided that those summaries contain sufficient information needed for evaluation of reliability (see below). Examples are the summaries prepared by industry within the context of REACH and the Assessment Reports for biocides that can be accessed via the European Chemicals Agency (ECHA[3,4]), and for plant protection products that are prepared by member states under EU regulation 1107/2009 and can be obtained from the European Food Safety Authority (EFSA[5]).

Please note that even though these data have been used within another framework, this does not mean that these data are automatically reliable within the context of the ERL derivation framework, and they should be evaluated according to the methodology as described below. When using summaries prepared in other frameworks, the citation of these data should always include the year in which these summaries were published. The year in which the study was conducted should be contained in the study summary.

5.1.1 Data sources

For the collection of ecotoxicity data, the following sources should preferably be used (not necessarily in the order presented here):

1. Previous ERL derivations by RIVM.
   For current standards available via https://rvs.rivm.nl/, or all reports via https://www.rivm.nl/publicaties
2. ERL derivations by regulatory agencies in other countries
   An overview of quality standards of various countries is available via a database of the German Umweltbundesamt at Search - ETOX: Informationssystem Ökotoxikologie und Umweltqualitätsziele. Several countries publish ERL derivations, risk assessment reports and/or datasheets on the web. Contact

[3] http://echa.europa.eu/information on chemicals
[4] http://www.echa.europa.eu/web/guest/information-on-chemicals/biocidal-active-substances
[5] http://www.efsa.europa.eu/en/pesticidespeerreview/assessmentreports.htm

persons are consulted for access to risk limit derivations and/or specific information on ecotoxicity.

3. Stakeholders
   Industry parties involved in production or use of the compound(s) under investigation are invited to submit relevant studies, which will be treated as public literature.

4. Open literature
   Relevant literature is retrieved by screening systems like Scopus or Web of Science. It is important to perform a retrospective literature search. The reference lists of publications or reports obtained should be carefully checked for related studies that have been published at earlier dates. A copy or pdf-file of each study that is deemed relevant should be obtained.

5. Databases
   a. The OECD eChem Portal connects to several databases with information on physical chemical properties, ecotoxicity, environmental fate and behaviour, toxicity. https://www.echemportal.org/echemportal/index.action
   b. The ECOTOX database from the US EPA [59]. A copy or pdf of the study report or peer-reviewed literature article underlying the results retrieved from this database is necessary to be able to assess the results. The database can be found at https://cfpub.epa.gov/ecotox/
   c. ECHA database https://echa.europa.eu/information-on-chemicals for information on substances that are registered under REACH.
   d. The database of the Japanese National Institute of Technology and Evaluation (NITE): https://www.nite.go.jp/index-e.html.

6. EU-Risk Assessment Reports
   Risk assessment reports (EU-RARs) published under the former Directive 67/548/EEC and following Regulation (EC) 1488/94, can be found at the ECHA website, https://echa.europa.eu/nl/information-on-chemicals. Note that some of the EU-RARs have not been finalised before REACH came into force and are indicated as so-called "Annex XV transitional reports". REACH registration dossiers may refer to data from RARs.

7. OECD assessments
   The OECD works with member countries and other stakeholders to cooperatively assess the hazards of industrial chemicals. The Screening Information Dataset (SIDS) documents can be found via the Existing Chemicals Database https://hpvchemicals.oecd.org/ui/Default.aspx. As for studies from other frameworks, studies included in the OECD SIDS documents are not automatically used without further evaluation.

8. Pesticides and biocides
   European assessment reports are available online at several locations.
   a. Draft Assessment Reports (DARs) and draft Renewal Assessment Reports (RARs) prepared for agricultural pesticides by EU member states in the context of European approval under 1107/2009/EC can be obtained via EFSA. The easiest way is to search for the active substance on the EFSA-website, the internet page with the conclusions of the peer review contains links to the underlying documentation. The final List of Endpoints is attached as Appendix or as supplemental information to the official publication in the EFSA-journal.
   b. Assessment Reports (ARs) prepared for biocides by EU member states in the context of European authorisation under 98/9/EC and 528/2012/EC can be obtained via https://echa.europa.eu/nl/information-on-chemicals or via https://www.echa.europa.eu/nl/information-on-chemicals/biocidal-active-substances.http://www.echa.europa.eu/web/guest/information-on-chemicals/biocidal-active-substances

   Assessment reports of individual countries may also be consulted. Evaluation reports from the US EPA may be retrieved via https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1, under the tab 'docket'
   evaluation report from Canada via https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates.html#erc-re.

9. Pharmaceuticals
   Information can be obtained from published assessment reports (EPARs or PuARs), at https://www.ema.europa.eu/en**Error! Hyperlink reference not valid.**. Also check https://www.fass.se/LIF/startpage and http://www.wikipharma.org/welcome.asp

If no or very few data are found in the steps described above, an additional internet search can be performed on the chemical name and CAS number of the compound using established search engines.

5.1.2 Type of data considered

For aquatic ERLs, ecotoxicity studies conducted in freshwater, seawater, and brackish water are potentially relevant and should be evaluated. For soil, experimental data on soil organisms are preferred, but if few data are available, ERLs are derived by equilibrium partitioning, meaning that all relevant aquatic data should be evaluated. A similar approach is followed for sediment. For groundwater organisms usually no experimental data are available, and aquatic ERLs are used as a substitute. ERLs for air are in most cases based on human-toxicological risk limits for inhalation, in rare cases specific information on ecosystem effects (e.g., plants) may be retrieved.

Whether or not data on secondary poisoning should be collected is dependent on the bioaccumulation potential. The literature should be searched for bioaccumulation data if the log K_{ow} value of the substance is equal to or larger than 3, or if there is any other indication of a bioaccumulation potential of the substance. Useful data sources for bioconcentration factors (BCF) are the physico-chemical properties and environmental fate handbook [15] and ECOTOX database [59]. In case assessment of secondary poisoning is triggered, toxicity data for birds and mammals should be collected, by screening the appropriate sources as described above. In the case of toxicity to birds, short-term 5-day LC50 studies should be collected too if no adequate chronic data on birds are available [60].

5.2 Data evaluation and selection: procedure and general aspects

This section gives general guidance on data evaluation and lists some aspects that are relevant for all environmental compartments.

5.2.1 Procedure

An outline of the general procedure of the evaluation of the ecotoxicity data is given below.

All retrieved literature is read and evaluated with respect to its usefulness and reliability (see 2.2). After evaluating a study, the results of the study are summarised by entering it into the appropriate data tables, see Annex 2.

In the ecotoxicity data tables, all tested species are clustered in taxonomic groups, according to the ERL report on taxonomy. Each row of the toxicity data table contains a test result for one species, endpoint and criterion. The columns of the toxicity data table contain the various study parameters. Columns should be filled as completely as possible. When there is no value for a given parameter, the table cell is left empty.

Data on aquatic, terrestrial, and benthic species are separated into acute and chronic data, with a separate table for each category. For aquatic ecotoxicity, data on freshwater organisms and data on marine organisms are placed in separate tables. Terrestrial toxicity data are divided into toxicity data on terrestrial species and data on terrestrial microbial processes and enzymatic reactions. Toxicity data on birds and mammals are also placed in separate tables. If many data are available, a distinction can be made between studies with oral dosing (capsule, gavage) and dietary (food) exposure. All references of ecotoxicity studies mentioned in the data tables should be included in one or more reference lists.

A series of toxicity data tables has now been created, the number of which depends on the compartments of interest (e.g., secondary poisoning may or may not have been triggered, etc.). Next, from each toxicity data table, the selected toxicity data are aggregated to *one toxicity value per species*. Such an aggregated data table is created for all compartments. The table will contain the data that are used for the

actual risk limit derivation. The guidance on compilation of this table is given in section 5.3.

5.2.2 Acute and chronic ecotoxicity data used for ERL derivation

In the context of ecotoxicological testing, the terms 'acute' and 'chronic' refer to the test duration in relation to the generation time of an organism and the endpoint studied. Acute and chronic can not be translated with the terms 'short-term' and 'long-term' as the latter indicate only the length of the exposure time in the toxicity test. E.g. short-term is days to one week, long-term is weeks to months. Note that this terminology allows for a border area where both terms may apply. Effect levels or no effect levels such as EC50 or NOEC can be derived from chronic as well as acute tests and may refer to lethal as well as sub-lethal parameters [61]. The principal ecotoxicological test results used in ERL derivation are EC50 or LC50 values from acute studies and NOEC, EC10 or LC10 values from chronic studies, the latter usually on sublethal endpoints. See Table 7 for an overview.

Within the context of this guidance, a chronic toxicity study is defined as a study in which:

1. the species is exposed to the toxicant for at least one complete life cycle, or
2. the species is exposed to the toxicant during one or more sensitive life stages.

This definition is in line with REACH and WFD guidance, which state that NOECs from chronic/long-term studies should preferably be derived from full life-cycle or multi-generation studies [2,60]. Hence, an acute study is a study in which the species is exposed to the toxicant for a part of its life cycle and not during a sensitive life stage. True chronic studies cover all sensitive life stages.

To decide on classification of tests in the ERL data tables (acute or chronic), the above definition of chronic is leading. If a study is not chronic following the definition, it is tabulated under the acute tests. E.g. a 14-day fish study, which is not an early life stage, embryo or developmental test. Considering the exposure duration only, such a test would perhaps be called a sub-chronic test, rather than 'acute'. For the sake of ERL derivation it classifies as 'acute'. On the other hand, ELS tests for fish, but also for other species such as amphibians (FETAX test), larval growth tests for molluscs (often performed with *Crassostrea* sp., but other species are used as well) or echinoderms, may be considered as chronic or sub-chronic toxicity studies, even if the duration of exposure is only a couple of days (see also [2]). This guidance cannot cover all cases and borderline cases have to be judged upon by expert judgement.

Tests with algae are short-term studies, i.e., lasting only a few days, but in view of the generation time of algae, the obtained endpoints refer to chronic rather than acute effects. However, due to the inability to maintain exponential growth in an algal culture for a longer period of time the EC50 of this test is used as an acute value, while the NOEC or EC10 of such a test is a chronic value (see [2]). A similar situation exists

for macrophytes, for which no separate guidelines are available for acute and chronic studies.

For terrestrial organisms, the division into acute and chronic is less clear, because the minimum duration of the available OECD tests is a few weeks. The LC50 from a 14-days earthworm study should be considered as an acute endpoint, while the NOEC for reproduction from a 56 day study is a chronic endpoint [11]. However, if a NOEC for mortality of adults is obtained from the first 4 weeks of this study, this is also considered as a chronic endpoint. For plants, the updated OECD guideline 208 is designed to assess the potential effects of substances on seedling emergence and growth. Therefore, it is specific to a part of the plants life-cycle and does not cover chronic effects or effects on reproduction, however it is assumed to cover a sensitive stage in the life-cycle of a plant and therefore data obtained form this study have been used as estimates of chronic toxicity [11].

The test results commonly encountered in ecotoxicological tests are summarised in Table 4 with guidance on their use (or not) in ERL derivation. For explanation of abbreviations please see the List of abbreviations. The most common endpoints are either EC50 or LC50 in the case of acute toxicity tests and EC10 or NOEC in the case of a chronic test. Other examples of endpoints that are regularly found in the literature are LOEC, MATC (the geometric mean of NOEC and LOEC) and TLm, which is equivalent to the LC50. If a NOEC is reported, the LOEC can be omitted from the reporting table. EC50 and LC50 values from chronic studies as well as NOEC and EC10 values from acute studies may be documented in the data tables, if this had added value (e.g., if no other data are available for a particular species).

If the endpoint presented is an ECx or LOEC value with an effect between 10 and 20% (i.e., x = 10-20), then a NOEC can be derived according to REACH Guidance R.10 (Table R.10-1), by dividing the ECx by a factor of 2 [60]. In such a case, the NOEC can be presented in the toxicity data table, with a note that this value is estimated from an ECx value. In a strict sense, calculating NOEC as ECx/2, according to REACH guidance, is only allowed for ECx values with an effect smaller than 20%. However, EC20 values are often presented in the literature. If there is no other information on the dose-response relationship (e.g. a companion EC50, which enables the calculation of an EC10), the EC20 divided by 2 can be considered as NOEC as well, accompanied by a footnote in the table with selected toxicity data (see section 5.3). However, in all cases, the information on a dose-response relationship must be used as much as possible. If it is possible to derive EC50 and EC10 values from a range of tabulated or graphically presented ECx values, these derived endpoints can be included in the toxicity data table as well, accompanied by a footnote stating the method of derivation.

Table 4 Criteria derived from toxicity studies and their use in ERL derivation – summary.

Test type	**Criterion**	**Use in ERL derivation?**	**Action**
acute test	EC50 or LC50	Yes	Tabulate value
acute test	NOEC, EC10 or LC10	No[a]	Tabulate value if valuable as additional information
acute test	ECx or LCx	No	Tabulate value if valuable as additional information
acute test	LOEC	No	Tabulate value if valuable as additional information
acute test	MATC[b]	No	Omit if NOEC is also available from same experiment Else: tabulate value if valuable as additional information
acute test	TLm	Yes	Tabulate as LC50[c]
chronic test	NOEC, EC10 or LC10	Yes	Tabulate value
chronic test	ECx (x < 10)	No	Omit if NOEC is also available from same experiment If more than one ECx value is available, try to establish an EC10 from a statistically reliable dose-response relationship Else: tabulate value if valuable as additional information
chronic test	ECx (10 < x < 20)	Yes	Omit if NOEC is also available from same experiment If more than one ECx value is available, try to establish an EC10 from a statistically reliable dose-response relationship Tabulate value if the ECx is the lowest effect concentration for a species. Calculate NOEC = ECx/2 (REACH Guidance ; Table R.10-1) and tabulate this NOEC[d]
chronic test	EC50 or LC50	No[a]	Tabulate value if valuable as additional information
chronic test	ECx (x ≥ 20)	No	Tabulate value if valuable as additional information If more than one ECx value is available, try to establish an EC10 from a statistically reliable dose-response relationship
chronic test	LOEC	No	Omit if NOEC is also available from same experiment Else: (i) if percentage effect is known, see ECx in this table for further guidance

Test type	Criterion	Use in ERL derivation?	Action
			Else: (ii) if percentage effect is unknown: tabulate value if valuable as additional information
chronic test	MATC[b] - single value, no further information	Yes	Omit if NOEC is also available from same experiment Else, if no further information is available, calculate NOEC = MATC/√2 (REACH Guidance ; Table R.10-1) and tabulate this NOEC[e]
chronic test	MATC[b] - reported as a range	Yes	Omit if NOEC is also available from same experiment Else, if no further information is available, tabulate the lowest value of the range as NOEC[f]
chronic test	MATC – spacing factor[g] is given[f]	Yes	Omit if NOEC is also available from same experiment Else, if no further information is available, calculate NOEC = MATC/√(spacing factor)[g] and tabulate this NOEC[h]

a: For toxicity tests with algae and Lemna sp., both the EC50 and the EC10 or NOEC are used in the ERL derivation, if available.
b: The MATC is the geometric mean of NOEC and LOEC.
c: A footnote should be added to the toxicity data table stating that the TLm is used as LC50.
d: A footnote should be added to the toxicity data table stating that the NOEC is calculated as ECx/2.
e: A footnote should be added to the toxicity data table stating that the NOEC is calculated as MATC/√2.
f: A footnote should be added to the toxicity data table stating that the lowest value of the MATC range is taken as NOEC.
g: The spacing factor is the factor of difference between two subsequent testing concentrations employed in the toxicity experiment.
h: A footnote should be added to the toxicity data table stating that the NOEC is calculated as MATC/√(spacing factor).

5.2.3 *Relevant ecotoxicity endpoints*

In general only those endpoints are considered that have consequences at the population level of the test species (see also WFD guidance). The list below shows some population-relevant parameters:

- growth (weight, length, growth rate, biomass)
- number (cells, population)
- mortality
- immobilisation
- reproduction
- hatching (rate, time, percentage)
- sex ratio
- development (egg, embryo, life stage)
- malformations (teratogenicity)
- proliferation (cells)
- filtration rate (bivalve molluscs)
- carbon uptake (algae)
- reburial (of e.g. certain crustacean species)

This list is not exhaustive. Demographic parameters (e.g. age distribution) and data from biomarkers may be used as endpoints if they are relevant in terms of population dynamics. Similarly, inhibition of photosynthesis in may be included as a marker for reduced viability of algae. Toxicity test results based on parameters for which the relationship to effects at the population level is uncertain or not established, are not used as a basis for ERL derivation. Some examples of endpoints where effects at population level are unclear include:

- blood or plasma protein levels,
- certain histopathological endpoints,
- organ weights (e.g. hepatosomatic index, gonadosomatic index),
- mRNA induction,
- endpoints determined *in vitro* tests,
- behavioural responses (e.g. swimming behaviour, antenna motility, etc.),
- coloration.

Note however, that the use of these types of endpoints for ERL derivation might be reconsidered when a definite correlation or causal relationship with an effect at the population level is established [2]. Regarding histopathology, clear effects on reproductive organs may be considered more closely related with population-level effects than changes in e.g. liver structure. This also holds for behavioural responses such as feeding and (in)ability to escape from predator attack.

In view of the increasing awareness among scientists of the ecological relevance of organismal behavioural, consideration of such endpoints in regulatory ecotoxicology has been promoted recently [62,63]. However, this has not yet resulted in the formal inclusion of such endpoints in regulatory guidance.

Based on an exploratory literature review on this topic, it was concluded previously that for fish and crustaceans sufficient evidence exists that effects on movement and feeding should be treated in a same manner

as ‘traditional’ response parameters such as growth and reproduction [64]. Available evidence from a meta-analysis demonstrates that the sensitivity of acute behavioural responses was more or less comparable to chronic effects on growth and reproduction. For species already present in the dataset with test results on growth and reproduction, inclusion of behavioural parameters may thus not lead to markedly different NOEC values. However, inclusion of such information may substantially increase the dataset with species for which those apical endpoints (e.g., growth, reproduction) are not available and may thus give a better picture of the variation in species sensitivity. The authors of the literature review advise to gather and graphically present all available information instead of starting an environmental risk assessment with eliminating information on ‘non-traditional’ parameters [64]. An example of such a graphical representation of results is given below (Figure 1). According to the authors, in such a case an ERL can still be based on traditional endpoints and at the same time be compared with additional information to judge whether the ERL is sufficiently protective. In addition, if effects are observed for parameters for which a relationship with population development has not (yet) been established, this may still be a reason to adapt the assessment factor if these effects appear at lower concentrations than the lowest valid endpoint.

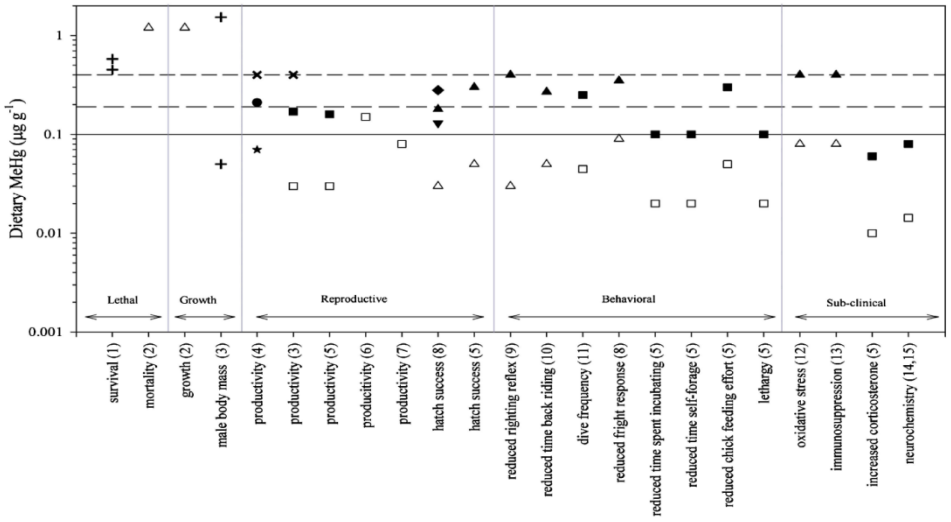

Figure 1 Graphical representation of data found in the literature for the effect of methyl mercury on different endpoints in the common loon Gavia immer*. Figure copied from [65].*

5.2.4 Toxicity values higher or lower than range of test concentration

If the highest concentration in an ecotoxicity test is not high enough to determine the NOEC or L(E)C50, the result of that study should be tabulated as 'NOEC ≥' or 'L(E)C50 >', followed by the value of the highest test concentration. This test result should be reported in the toxicity data tables, but is not used as a basis for the ERLs. However, it is valuable information that a species from this taxon (or trophic level) has been tested and that it was not sensitive to the toxicant at a known concentration, especially when the data set is limited. Because of this, the presence of this toxicity value may influence the height of the

assessment factor. For example: when NOEC values for algae, *Daphnia* and fish are found, of which one is a 'NOEC ≥' value, and this value is not the lowest effect concentration, an assessment factor of 10 may be applied, whereas this would have been 50 if the study had been rejected. For similar reasons, data from tests resulting in an effect at the lowest test concentration should be tabulated as NOEC < or L(E)C50 <, followed by the value of the lowest test concentration. Although these values may not be used directly for the derivation of the risk limits in a deterministic approach, the information is useful to compare the sensitivity of that specific species with the derived risk limit. This comparison may influence the choice for the final assessment factor that is applied for the derivation of the risk limit. Moreover, statistical techniques have become available that allow for the inclusion of censored data in SSDs [66].

5.2.5 Purity and identity of the test substance

In some tests the identity of the test substance is largely unknown or the purity of the test substance is very low. Depending on the nature of the impurities present, if these have been identified at all, a minimum purity of 80% is required, unless it is known that the impurities do not cause any toxic effects by themselves and do not influence the toxicity of the substance of interest. When the purity of the tested compound is < 90%, the test result should be corrected for purity. For technical mixtures of compounds of which a substantial fraction (impurity) consists of one or more compounds structurally related to the test compound, it is subject to expert judgement whether the test result is useful for risk limit derivation or not. For pesticides, toxicity should be expressed in terms of the concentration of active ingredient. If a formulation has been tested, but due to missing information it is not possible to express the endpoint on the basis of the active ingredient, the study is assigned Ri 3 (see section 2.2).

5.2.6 Use of co-solvents, emulsifiers and dispersants, formulated products

Sometimes, the solubility of a compound is so low that a solvent, emulsifier or dispersant is used to prepare suitably concentrated stock solutions of the test substances. Such vehicles may not be used to enhance the solubility of the test substance in the test medium, and in any case the compounds used for this purpose may not be toxic to the tested species. Therefore, a control with the vehicle (solvent control) used should be incorporated in the set-up of the test. According to several OECD test guidelines for aquatic toxicity testing, the concentrations of the solvent, emulsifier or dispersant should not exceed 100 mg/L (or 100 µg/mL or 0.01%). In terrestrial studies, a common procedure for addition of substances that are insoluble in water is to add the compound as a solution in acetone, after which the vessels are left overnight to let the solvent evaporate (e.g., OECD guidelines 207, 232).

For derivation of ERLs for pesticides, studies with the active ingredient are considered most appropriate. Effects of formulations, if present, will be relevant shortly after application and in the near vicinity of the site of use, but less so for generic long-term quality standards. When for a given species results are available from similar tests with the active and with formulations (for comparable endpoints), it should be determined whether or not the results can be pooled. Recently, it was proposed to

use the geometric mean of the available values for studies with the active ingredient only and studies with formulations, if the standard deviation of the log-transformed individual toxicity values is <0.5 [61]. However, further analysis of this proposal reveals that with small datasets, endpoints differing by more than a factor of 10 can also meet this criterion. Therefore a more arbitrary cut-off value is advised: if the endpoints for studies with formulations and studies with the active ingredient only differ by more than a factor of 3, the value of the studies with the active ingredient is used, also when this results in a higher value. However, if for a species the most critical endpoint originates from a test with a formulated product, and no comparable endpoint from a test with the active substance is available, this endpoint of the formulation is used for risk limit derivation.

5.2.7 Comparison of toxicity values with water solubility

In principle, toxicity studies that have been conducted at concentrations above the water solubility should not be used for ERL derivation. However, depending on the uncertainty in the estimate of the water solubility (see section 4.2.3 on how to determine and choose solubility values), test results (L(E)C50, NOEC, EC10) that are ≤ 2 times the estimated solubility value might be included in the risk assessment. The factor of 2 is a rather arbitrary value; when experimental data show that the variation in the estimate of the water solubility is lower, it should be lowered accordingly. When the variation in the estimate of the water solubility is higher than a factor of 2, it may be increased to a factor of 3 (maximum). Toxicity studies showing results above the water solubility receive a footnote stating: 'test result above water solubility'. For terrestrial studies, it should be considered if saturation of pore water has been likely at the soil concentrations tested. When deriving ERLs for PAHs, it was concluded that some NOECs expressed on the basis of total soil concentrations were of limited relevance, because pore water was already saturated at levels far below the concentrations used in the test [67].

5.2.8 pH, pK_a and ionisation of test compound

When a test has been performed according to a guideline, the pH should be within the required range for this test and, if not, it should be checked whether the test can still be considered valid. Expert judgement should be employed to determine if a test result should be excluded. A test may become invalid because the test organisms naturally occur at other pH values. For non-standard guideline studies, expert judgement is needed to decide on this.

In some cases, the compound itself may alter the pH strongly. In such cases, it should always be checked whether the observed toxicity might be caused by this change in pH. If so, the test must be considered as invalid, because the buffering capacity of the environment will prevent such a pH effect in the field. For compounds containing functional groups with acidic or basic properties, the pK_a value(s) should be reported in the table with physico-chemical properties (section 4.2, Table 3). Attention should be paid to possible relationships between pH and toxicity of the tested compound, for example, due to a reduced availability (speciation, precipitation, hydrolysis, etc.) of the test compound. The toxicity of a compound may be influenced by its degree

of ionisation[6]. Hydrophobicity, and consequently solubility and bioavailability of a given compound may vary dramatically even within an environmentally relevant pH range [68]. In general, neutral forms tend to be more toxic than ionised forms. However, since uptake may also be influenced by the degree of ionisation, the net effect on toxicity may differ. The degree of ionisation of a compound in a toxicity test therefore is an important factor which is determined by several factors:

- the pKa value(s) of the test compound,
- the concentration of the test compound,
- pH of the test compartment (soil, water, sediment),
- the buffering capacity of the test-matrix.

In practice:

- a compound's potential to ionise (pK_a in physico-chemical table) should be checked (see also section 4.2.4);
- presence of one or more pKa value(s), or ionisable group(s), triggers the attention for pH effects in toxicity studies;
- if toxicity test results reveal that toxicity is dependent on the pH of the test-matrix (soil, water, sediment), it might be considered to reject test results if the pH falls outside the range of what can be expected naturally.

Test results should be rejected when it can be inferred that the toxicity in a given study is not caused by the compound alone, but also by a pH change. Hence, results from tests with ionisable compounds performed in buffered media (providing sufficient buffering capacity) may be considered more reliable than those performed without a buffer. Those studies that explicitly mention a measured pH after addition of the toxicant are most useful in this respect.

5.2.9 Ecotoxicity studies performed in other media

For the purpose of ERL derivation, only studies are considered in which the species are tested in medium that resembles their natural habitat. If this is not the case, as for example with terrestrial plant toxicity studies that were conducted in nutrient solution or toxicity studies with earthworms on filter paper, these studies are not used as a basis for ERL derivation. Effect concentrations for terrestrial species should be expressed in weight units per kg dry soil, and this is impossible when a study was conducted in water or filter paper. Generally, these studies are not reported in the data tables in which all toxicity studies are collected, but they may still be used for purposes of comparison.

Terrestrial species tested in nutrient solutions can be compared with aquatic species if equilibrium partitioning is used to derive the environmental risk limits for soil. If data on aquatic macrophytes are missing, terrestrial plant species tested in water may give an indication of the expected (in)sensitivity and be used for justification of assessment factors or to judge if an SSD may be constructed despite a missing taxon.

[6] 'Degree of ionisation' as used in this section expresses the ratio of the number of charged molecules over the total umber of neutral and charged molecules at a given concentration and at a given pH.

In some terrestrial toxicity studies, concentrations in pore water are reported. Results from these studies can only be used if truly dissolved concentrations have been measured (e.g. by SPME or SPMD techniques). Analyses in pore water obtained after centrifugation are not useful in this respect since the water fraction obtained in this way may still contain a fraction of a substance associated with DOC, or associated with the POC fraction that is too light to be centrifuged or a fraction of substance in colloidal form, if applicable to the substance in question. Equilibrium partitioning should be applied to the pore water concentration, in order to calculate a concentration in soil that can be used in ERL derivation.

Benthic species are often tested in a water-only system or a system with inert substrates (e.g. glass beads, quartz sand). In such cases the data are still tabulated, and may be used for derivation of risk limits for water.

5.3 Selection and aggregation of laboratory ecotoxicity data

One toxicity value per species is selected/calculated for use in the assessments. Where multiple data are available for the same species/endpoints that are obtained under comparable test conditions, individual toxicity data may be aggregated using the same principles as those in Chapter R.10 of the REACH Guidance [60]. Below, some general points are listed which should be considered when grouping data per species, based on several guidance documents [1,60,61,68,69]. For specific items, see also the ERL documents on water, sediment and soil.

1. Identify particularly sensitive species and/or endpoints that may be lost upon averaging data to single values.

2. Investigate multiple values for the same endpoint on a case by case basis and look for the cause of differences between results.

3. Where valid data show high variation that can be explained, grouping of data is considered, e.g., by pH ranges.

4. If an effect of test conditions is expected to be the cause of variation in toxicity values, averaging of data per species should not be performed. Examples are: hardness of test water, life stage of the test animal, pH, clay content of soil, test duration, bioavailability governed by interactions other than hydrophobic sorption alone, etc.

5. For non-standard test species, preference is given to endpoints for parameters that are applicable to related standard test species, e.g. immobility for non-standard crustaceans or reproduction of non-standard worm species. Whether or not non-standard endpoints can be included in the dataset has to be judged on a case-by-case basis.

6. If results are available from test(s) with different exposure durations, preference is given to the results from tests that followed the (minimum) test duration as specified in the

guideline. E.g. when an EC10 for algal growth rate after 24, 48 and 72 h exposure is available, the 72 h result will be used when this is consistent with an existing guideline. The same holds when a 24 h EC10 after and a 72 h EC10 are available for the same species but from different tests. Both studies and results are tabulated, but the 72 h value is preferred and selected for use in ERL derivation[7].

7. Data for derivation of ERLs should be selected on the relevance of test conditions (pH, hardness, etc.) to the field. However, deselection of data on the basis of presumed irrelevant test conditions should only be done if it is clear that the conditions have a major influence on the test result.

8. If the variation in test results of different life stages of a test animal is such that averaging data would cause significant under-protection of sensitive life stages, only the data for the most sensitive life stage should be selected. In other words, it is important that sensitive life stages are protected.

9. If differences in the chemical form of the test compound (congeners, stereoisomers, etc.) are the cause of variation in toxicity values for a test species, data should not be averaged. In these cases, separate ERLs should be derived for each chemical form.

10. Based on the aforementioned considerations, calculate the geometric mean of multiple comparable toxicity values for the same species and the same endpoint. This applies to both acute and chronic data.

11. If multiple toxicity values or geometric means for different endpoints are available for one species, the most sensitive endpoint is selected as long as it is relevant to population sustainability. If multiple valid toxicity data for one species are left that cannot be averaged, the lowest value is selected.

Example. There are values (NOECs or EC10 values) for three different endpoints, derived from several chronic studies with *Daphnia magna*. The geometric mean of NOECs for reproduction is 0.49 mg/L, the geometric mean of NOECs for mortality = 3.1 mg/L and there is a single EC10 value for growth of 0.67 mg/L. The geometric mean value of 0.49 mg/L for reproduction is selected for use in ERL derivation.

The aggregated data should be presented in a new table. The selected acute and chronic values are presented separately for each species, and a footnote is added to explain how the value is derived from the summary data tables.

[7] Prerequisite for this is that exposure to the test substance is well identified in both tests.

6 Human toxicological threshold limits

A human toxicological threshold value (TTL_{hh}) is needed at several places in ERL derivation:

- in the derivation of the water quality standard for surface waters based on human consumption of fishery products ($QS_{water,\ hh\ food}$)
- in the derivation of the quality standard for surface water intended for drinking water abstraction ($QS_{dw,\ hh}$)
- in the derivation of the risk limits for soil based on indirect exposure of humans [83].
- in the derivation of ERLs for air

For derivation of MPC_{air}, the TCA (Tolerable Concentration in Air) is used or the $CR_{inhalation}$ (inhalatory Cancer Risk) for genotoxic carcinogens. See section 2.1 of ERL guidance for air.

For the other three ERLs listed above, the TTL_{hh} values that can be used are the ADI (acceptable daily intake) and the TDI (tolerable daily intake). The US ATSDR uses the term MRL (minimum risk level) while the US EPA uses the term RfD (reference dose). A list of organisations or frameworks that have published human toxicological threshold limits is presented in Table 10.

In general, it is advised to take the most recent value and consult a human toxicologist on the final choice of the value. If a clear value is reported in a European risk assessment report, or a value for TTL_{hh} is derived in the Netherlands (often denoted as MPC_{human} or MPR_{human}), these values should preferably be used because of consistency with other national frameworks. However, a human toxicologist should be consulted to check if new data exist that require updating of those values. For substances for which a threshold level cannot be given (e.g. genotoxic carcinogens), unit risk values corresponding to an additional cancer risk may be used, if available. The risk levels to be used for the respective compartments are explained in the specific chapters.

In recent years, overarching databases have become available. These systems give access to existing (inter)national databases with toxicological information, including most of the abovementioned ones. A possible starting point to obtain relevant information is the eChemPortal (https://www.echemportal.org/echemportal/index.actionhttp://www.echemportal.org/echemportal/page.action?pageID=0). A non-limitative selection of other information sources is listed below.

Table 5 Sources for the retrieval of human toxicological threshold limits.

Source name and publisher	Available at
ATSDR Toxicological Profiles (ATSDR)	Toxicological Profiles | Toxicological Profiles | ATSDR
ADIs for pesticides	EU Pesticides Database - European Commission
IPCS (CICAD)	IPCS INCHEM - Concise International Chemical Assessment Documents (CICADs)
DWQG (WHO)	Water Sanitation and Health
EFSA	http://www.efsa.europa.eu/
Environmental Health Criteria (EHC) (WHO/IPCS)	IPCS INCHEM - Environmental Health Criteria Monographs
HSDB (NLM/NIH)	PubChem
HSG (WHO)	http://www.inchem.org/pages/hsg.html
IARC Monographs (WHO)	IARC Monographs on the Identification of Carcinogenic Hazards to Humans – INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
ICSC (IPCS-EU)	http://www.inchem.org/pages/icsc.html
IRIS (US EPA)	Integrated Risk Information System | US EPA
ITER (TERA)	ITER
JECFA Monographs (WHO/FAO)	IPCS INCHEM - Joint Expert Committee on Food Additives (JECFA) - Monographs & Evaluations
JMPR Monographs (WHO/FAO)	IPCS INCHEM - Joint Meeting on Pesticide Residues - Monographs & Evaluations
OEHHA Toxicity Criteria Database (Cal-EPA)	Chemicals - OEHHA
RIVM	https://rvs.rivm.nl/#
RIVM: MPC_{human} values for the derivation of SRC_{human}	https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf
SIDS (OECD-UNEP)	OECD's Work on Co-operating in the Investigation of High Production Volume Chemicals - HPV Database search
WHO Air Quality Guidelines	WHO Ambient Air Quality Database (Update Jan 2024)

#: this website does not contain a list of ADI- or TDI-values, but can be used to find documentation on the substance of concern.

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List of abbreviations

ADI	acceptable daily intake
AF	assessment factor
a.i.	active ingredient
US ATSDR	United States Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstract Service
ClogP	calculated log octanol/water partitioning coefficient by the software program BioLoom [17]
d	days
DFI	daily food intake
DT50	dissipation time for 50% of the substance
DWQG	drinking water quality guidelines
EC	European Commission
ECHA	European Chemicals Agency
EC_x	effect concentration at which an effect of x% is observed, generally EC10 and EC50 are calculated
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
ELS	early life stage
EPAR	European public assessment report (pharmaceuticals)
EPI suite	estimation programs interface suite
EPICS	equilibrium partitioning in closed systems
ERL	environmental risk limit
EU	European Union
EU-RAR	European Union-Risk Assessment Report in the context of the former the former Directive 67/548/EEC and following Regulation (EC) 1488/94
FAO	Food and Agriculture Organisation
FETAX	frog embryo teratogenesis assay
GC	gas chromatography
GLP	Good Laboratory Practice
h	hours
HPLC	high performance liquid chromatography
HSDB	hazardous substances databank
HSG	health and safety guides
IARC	International Agency for Research on Cancer
ICSC	International Chemical Safety Cards
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
ITER	International Toxicity Estimates for Risk assessment
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
LC_x	effect concentration at which x% lethality is observed, generally LC50 and LC10 are calculated
LOEC	lowest observed effect concentration
MATC	maximum acceptable toxicant concentration
MCI	molecular connectivity indices

MlogP	measured log octanol/water partitioning coefficient selected by the software program BioLoom
mo	months
MPC	maximum permissible concentration
MPR	maximum permissible risk level
MRL	minimum risk level
mRNA	messenger ribonucleic acid
NIH	national institutes of health
NITE	(Japanese) National Institute of Technology and Evaluation
NLM	National Library of Medicine
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
oc	organic carbon
OECD	Organization for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment
om	organic matter
PAH	polycyclic aromatic hydrocarbon
PCB	polychlorinated biphenyl
QS	quality standard
QSAR	quantitative structure activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical substances.
RfD	reference dose
Ri	reliability index
RIVM	National Institute for Public Health and the Environment
SIDS	screening information data set (OECD)
SMILES	simplified molecular input line entry system
sp.	species
SPMD	semi permeable membrane device
SPME	solid phase micro extraction
SRC	Syracuse Research Company
SRC_{human}	serious risk concentration for humans
SSD	species sensitivity distribution
TDI	tolerable daily intake
TERA	Toxicology Excellence for Risk Assessment
TGD	Technical Guidance Document
TL_{hh}	threshold level for human health
TL_m	median tolerance limit; also encountered as: median threshold limit
US EPA	United States Environmental Protection Agency
w	Weeks
WAF	water accommodated fraction
WFD	Water Framework Directive
WHO	World Health Organization
y	Years

Annex 1. Partition coefficients – glossary

This appendix gives a brief overview of terminology and equations used with respect to partition coefficients encountered in soil and sediment adsorption studies.

In the field of environmental chemistry and ecotoxicology, the distribution of a compound over two different environmental compartments is commonly described using an equilibrium constant, expressed by the capital letter *K*. The equilibrium constant describes a ratio of concentrations of a chemical compound in two different phases, similar to the description of the dissociation constant of acids and bases at equilibrium (usually pK_a).

Since the solute solvent sorbent system is assumed to be in thermodynamic equilibrium, *K* can be considered a constant; however, it is valid only for the conditions (pH, temperature, concentration range, type of sorbent, etc.) employed during its determination. To illustrate that the ratio refers to the *distribution* of a compound over two phases rather than a concentration ratio in identical phases, a subscript d (for distribution) is added: K_d.

The term *partitioning* is also used to describe the distribution of a compound over different phases, e.g. when describing the partitioning of a compound between octanol and water: K_{ow}. The same parameter is also found as P_{ow}.

In practice, distribution constants of metals between water and soil (or sediment, or suspended matter) are often expressed as K_p values, and are then referred to as partition coefficients (rather than constants). In fact, both K_d and K_p are used here to describe the same process (i.e. adsorption) and can be seen as synonyms. In the pesticide registration framework, $K_{s/l}$ is also used to describe the same parameter and is called solid/liquid partition coefficient.

When sorption is independent of the concentration of the compound of interest, the sorption isotherm[8] is linear and K_d is calculated as follows:

$$K_d = K_p = \frac{C_s}{C_w} \qquad (8)$$

in which
- K_d and K_p are the linear distribution coefficient, linear partition coefficient or simply: linear sorption coefficient [L/kg]
- C_s is the concentration in the solid phase [mg/kg]
- C_w is the concentration in the aqueous phase [mg/L]

The units presented are those most commonly encountered in scientific literature, but different units may also be used.

[8] A sorption isotherm is the relationship between the adsorbed concentration (dependent variable) and the dissolved concentration of a compound, determined at a constant temperature.

The relationship most often used to describe non linear sorption is the (empirical) Freundlich model:

$$C_s = K_f \times C_w^{\frac{1}{n}} \qquad (9)$$

in which
- K_f is the Freundlich sorption coefficient [L/kg, when $^1/_n=1$[9]]
- n is an empirically determined parameter [-]

When n = 1, sorption is linear and $K_f = K_d$. When n > 1, the sorption isotherm is curved downward, with n < 1, the sorption isotherm is curved upward. It is not possible to specifically address the causes of non linearity of sorption isotherms. Both compound properties and sorbent characteristics influence sorption behaviour and at present, no general agreement exists on the mechanism(s) of sorption (Ten Hulscher, 2005).

Linearity or non linearity of sorption can be investigated by plotting logarithms of C_s versus logarithms of C_w. The slope of the linear function fitted through the data points is $^1/_n$ and the logarithmic form of equation **Error! Reference source not found.** is a linear relationship when n = 1. In evaluating adsorption studies in the framework of Dutch pesticide registration, K_f values are considered acceptable when $^1/_n$ is within the range of 0.7 – 1.1 [7]. We refer to Mensink *et al*. for quality criteria when reviewing batch adsorption studies.

K_f values are accepted as K_d values without correction when $^1/_n$ values are within the range of 0.7 – 1.1. K_f values with $^1/_n$ values outside the range of 0.7 – 1.1 are considered unreliable and are not used for ERL derivation.

For many organic compounds (in particular, neutral hydrophobic compounds), the sorption constant is directly proportional to the quantity of organic matter of the sorbent (Boethling and Mackay, 2000). K_p can then be normalised to the organic carbon content of the sorbent:

$$K_{oc} = \frac{K_p}{F_{oc}} \qquad (101)$$

in which
- K_{oc} is organic carbon normalised sorption coefficient [L/kg_{oc}]
- K_p is the partition coefficient [L/kg_{dw}]
- F_{oc} is the fraction organic carbon of the sorbent [kg_{oc}/kg_{dw}]

When the percentage of organic carbon of the sorbent is not reported it can be calculated from the percentage organic matter using a conversion factor. In equation:

$$\%\text{o.c.} = \frac{\%\text{o.m.}}{1.7} \qquad (11)$$

[9] When $^1/_n \neq 1$, K_f has the unit $L^{1/n}.mg^{1-1/n}/kg$.

in which
- % o.c. is the percentage organic carbon of the sorbent [% (w/w)]
- % o.m. is the percentage organic matter of the sorbent [% (w/w)]
- 1.7 is a conversion factor representing the ratio of soil organic matter content over organic carbon content [kg_{om}/kg_{oc}]

As a general rule it is assumed that organic matter contains 1/1.7× 100% = 58.8% organic carbon.

Annex 2. Examples of data tables

Table A2.1 Example of an ecotoxicity datatable: freshwater organisms.

Legend to column headings	
Species properties	relevant characteristics of the test species, such as age, size, origin
A	test water analysed Y(es)/N(o)
Test type	S = static; R = renewal; F = flow through; c = closed
Purity	refers to purity of active substance or content of active substance in formulation; ag = analytical grade; tg = technical grade
Test water	am = artificial medium; dtw = dechlorinated tap water; dw = deionised/dechlorinated/distilled water; nw = natural water; rw = reconstituted water; rtw = reconstituted tap water; tw = tap water
T	temperature
Ri	Reliability index according. Valid studies (Ri 2 or higher) are considered for EQS-derivation, depending on relevance and considering notes on data treatment

Species	Species properties	A	Test type	Test compound	Purity [%]	Test water	T [°C]	pH	Hardness $CaCO_3$ [mg/L]	Exp. time	Criterion	Endpoint	Value [µg/L]	Ri	Note	Ref.
Bacteria																
Vibrio fischeri	strain NRRL-B-11,177	Y	S	active	ag		15			30 min	EC50	bioluminescence	61900	2	1	[a]
Cyanobacteria																
Anabaena flos-aquae		Y	S	product A	200 g/L					96 h	EC50		32800	4	2	[b]
Algae																
Desmodesmus subspicatus		Y	S	active	ag		21			72 h	EC50	growth rate	389000	2	3	[c]
Scenedesmus subspicatus	10000 cells/mL	N	S	active	tg		23	8.2-9.1		72 h	EC50	biomass	> 10000	3	4	[d]
Crustacea																
Asellus aquaticus	field collected	N		product A	200 g/L	am	10			1 h	NOEC	respiration	100	3	5	
Ceriodaphnia dubia	< 24 h	Y	S	product B	42.8%	dw	25		80-100	48 h	LC50	mortality	2.07	2	6	
Insecta																
Aedes aegypti	4th instar	N	S	active	97.4	dw	25			72 h	LC50	mortality	84	3	7	
Baetis rhodani	larvae, field collected	N	S	active	ag	am	15	7.4	180	48 h	LC50	mortality	8.49	3	8	
Amphibia																
Rana limnocharis	1 month old	N	R	active	> 95%	dw	20			96 h	LC50	mortality	82000	3	9	
Rana N. Hallowell	1.5 months old	N	R	active	> 95%	dw	20			96 h	LC50	mortality	129000	3	10	
Pisces																
Danio rerio		Y	S	active	ag	nw	21	8.4	140	96 h	LC50	mortality	241000	2	11	
Danio rerio		Y	S	product C	200 g/L	nw	21	8.4	140	96 h	LC50	mortality	214000	2	12	

Notes
1 Marine species, but tested in distilled water. Stability of test concentrations in distilled water checked for 21 d at 21ºC, room light. At 70 mg/L and lower stable for 21 d, at 105 and 140 mg/L stable for 17 d, thereafter decline to 84 and 76% of nominal, respectively.
2 Solvent 1% DMSO, solvent control included; no analysis of test concentrations, but short exposure time
3 etc.

Table A2.2 Example of an ecotoxicity datatable: marine organisms..

Species	Species properties	A	Test type	Test compound	Purity [%]	Test water	T [°C]	pH	Salinity [‰]	Exp. time	Criterion	Endpoint	Value [µg/L]	Ri	Note	Ref.

Table A2.3 Example of an ecotoxicity datatable: soil organisms.

Legend to column headings	
Species properties	relevant characteristics of the test species, such as age, size, origin
A	test substance analysed Y(es)/N(o)
Purity	refers to purity of active substance or content of active substance in formulation; ag = analytical grade; tg = technical grade; rg = reagent grade
Test medium	artificial, natural soil, location
T	temperature
o.m.	organic matter content
st. soil	standard soil
Ri	Reliability index according. Valid studies (Ri 2 or higher) are considered for EQS-derivation, depending on relevance and considering notes on data treatment

Species	Species properties	A	Test compound	Purity [%]	Test medium	T [°C]	pH	o.m. [‰ dwt]	clay [%]	Exp. time	Criterion	Endpoint	Value test soil [mg/kg]	Value st. soil [mg/kg]	Ri	Note	Ref.

Table A2.4 Example of an ecotoxicity datatable: sediment organisms.

Species	Species properties	A	Test compound	Purity [%]	Sediment type/location	T [°C]	pH	o.m. [%]	clay [%]	Exp. time	Criterion	Endpoint	Value test sed. [mg/kg$_{dwt}$]	Value st. sed. [mg/kg$_{dwt}$]	Ri	Note	Ref.
Annelida																	
Lumbriculus variegatus	ad	Y	active	98%	natural sediment, Drontermeer, NL	20±1	6.2	12-14	16	28	EC50	reproduction	83	64	2	1,2,3	[a]

Table A2.5 Example of an ecotoxicity datatable: birds and mammals.

Legend to column headings	
Species properties	relevant characteristics of the test species, such as sex, age, size, origin
Purity	refers to purity of active substance or content of active substance in formulation; ag = analytical grade; tg = technical grade
Appl. Route	diet = dietary; water = drinking water; gav = oral gavage (intubation); caps = oral capsule
DFI	Daily Food Intake
Ri	Reliability index. Valid studies (Ri 2 or higher) are considered for ERL derivation

Species	Species properties	Test compound	Purity [%]	Appl. route	Vehicle	Diet type	Energy content [kJ/g$_{dw}$]	DFI [kg$_{food}$/kg$_{bw}$/d]	Duration	Exp. time	Criterion	Endpoint	Value [mg/kg$_{bw}$/d]	Value [mg/kg$_{fd}$]	Value [mg/kJ]	Ri	Note	Ref.