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Framework on Exposure-Based Adaptation of (human health) REACH hazard information requirements

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Framework on Exposure-Based Adaptation of (human health) REACH hazard information requirements

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SUMMARY

This report outlines the development of a practical and scientifically grounded framework for Exposure-Based Adaptation (EBA) under the REACH legislation, focusing specifically on human health endpoints. REACH mandates that registrants provide data on chemical hazards to enable accurate risk assessments and define appropriate risk management measures. However, when human or environmental exposure is absent or negligible, EBA provides an avenue to adapt or waive some of these data requirements. This not only streamlines compliance but also aligns with ethical efforts to reduce animal testing.

The European Chemicals Agency (ECHA) introduced the concept of EBA in 2011 through its Guidance R.5. While the guidance supported the idea of adapting information requirements based on exposure, it lacked quantitative metrics and detailed methodological direction. Consequently, registrants have applied EBA inconsistently, leading to varied regulatory acceptance.

Recognizing this gap, Concawe, in collaboration with Fraunhofer ITEM and several industry stakeholders, sought to establish a robust framework that could support EBA justifications with greater clarity and scientific rigor. Their work is focused primarily on three key endpoints where EBA is considered permissible: the 28-day repeated dose toxicity study, the 90-day sub-chronic toxicity study, and reproductive or developmental toxicity studies. The framework was shaped by a comprehensive review of the scientific and regulatory landscape, including major workshops and literature on exposure modelling, threshold concepts (like the TTC), and toxicokinetics.

A critical outcome of the review was the realization that terms such as “absence,” “negligible,” and “limited” exposure were inconsistently defined across documents and practices. This ambiguity has led to discrepancies in how EBA is implemented and accepted. As such, the framework includes refined definitions and standardization of terminology as a foundational element.

The EBA framework developed in this report is organized into a four-step process:

- **Step 1: Information Collection**
  - Gather all relevant substance data, including physicochemical properties.
  - Define use conditions and exposure scenarios.
  - Compile any available exposure monitoring or modelling results.
- **Step 2: Route of Justification Selection**
  - Choose one of three justification routes based on the availability of data and use conditions:
    - *Weight of Evidence (WoE)*: Qualitative assessment based on properties and usage.
    - *Quantitative Justification*: Comparison between predicted exposure and DNELs to demonstrate an acceptable Margin of Exposure (MoE).
    - *Strictly Controlled Conditions (SCC)*: Applicable when the substance is used in non-dispersive settings (note: outside the scope of this report).
- **Step 3: Justification Development**
  - Build the scientific rationale using exposure estimates, toxicological thresholds, and substance-specific factors.

    - Address the relevant exposure route(s) with supporting evidence or models.
- **Step 4: Summary and Illustration**
    - Present the justification in a format aligned with REACH R.5, using flow diagrams and narrative rationale.
    - Tailor the summary to specific use cases.

To enable clear and consistent justifications, the framework provides both toxicological and exposure-based thresholds. These criteria help determine whether exposure is truly negligible or absent:

- **Toxicological Thresholds**
    - Use **NOAELs** and derived DNELs for quantitative assessments.
    - Apply **TTC values** when DNELs are unavailable:
        - Inhalation (low toxicity): 0.05 ppm/day
        - Inhalation (high toxicity): 2×10^{-5} ppm/day
        - Oral exposure: 90 µg/person/day
- **Exposure Cut-Offs**
    - **Inhalation**: Vapour pressures below 0.01 Pa suggest minimal exposure risk.
    - **Dermal**: Maximum expected skin loading is compared to dermal TTC values (e.g., 2.5 µg/kg/day for high-toxicity substances). Fast evaporation rates or limited skin contact can support negligible exposure claims.
    - **Oral**: Water solubility less than 45 µg/L may indicate negligible exposure via drinking water. Residue levels in food can also be evaluated using established MRLs or regulatory thresholds.

These criteria can be applied qualitatively or quantitatively depending on the available data. When using the WoE route, the framework advises incorporating conservative assumptions and worst-case exposure scenarios, supported by models such as ECETOC TRA and IHSkinPerm. In cases of significant uncertainty, a higher margin of exposure—up to a factor of 1000—is recommended to ensure confidence in the justification.

Notably, UVCB (unknown or variable composition, complex reaction products or biological materials) petroleum substances were considered for EBA evaluation. However, it was determined that EBA is not meaningfully applicable due the compositional complexity of the substances and to Uses of these substances resulting in inevitable exposure.

Overall, this framework is intended to improve the quality and reliability of EBA justifications and should contribute to a better acceptance of these justifications for the purposes of risk assessment and the resulting identification of appropriate risk management measures.

KEYWORDS

Exposure based adaptation, REACH hazard information requirements, human health risk assessment, weight of evidence approach, Threshold of Toxicological Concern, waiving animal testing, likely route of human exposure.

INTERNET

This report is available as an PDF file on the Concawe website (www.concawe.eu).

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1. INTRODUCTION

REACH requires registrants to have hazard data on all endpoints pre-requisite to perform an appropriate chemical risk assessment and identify the risk management measures. However, exposure-based adaptation (EBA) may be considered in situations where exposure of humans or the environment is absent or so low that additional effects information will not lead to improvement of risk management (ECHA 2011). The terminology 'adaptation' comprises all types of modifications of the standard information requirements, including omissions, triggering, replacement or other adaptations (ECHA 2011). EBA can be used to justify the deviation from the standard information requirement.

ECHA developed in 2011 an explanatory guidance (R.5) on how to interpret EBA arguments introduced in REACH (ECHA 2011). This EBA guidance is presented in a general way, and does not provide quantitative metric for the generally accepted absence or negligibility of exposure. Registrants can develop their own scientific arguments with the risk that these would not be accepted by ECHA or result in inconsistencies in justifying the adaptations between substances.

The objective of this project was to review the available material on EBA for human health toxicity studies and develop a practical guidance/framework embracing the essential elements that need to be addressed when developing the EBA justification.

The project is divided into two stages: In a first stage it was agreed to focus on human health, where EBA may be considered according to R.5 guidance for the three endpoints of short-term repeated dose toxicity study (28 days), sub-chronic toxicity study (90 days), and reproductive / developmental toxicity. In the future, this framework could be upgraded to include adaptation information requirements for environmental hazard endpoints.

2. AVAILABLE INFORMATION ON EXPOSURE BASED ADAPTATION (EBA)

2.1. SCIENTIFIC AND GREY LITERATURE

The scientific and grey literature search resulted in compilation of information from several workshops (BfR 2010; Bunke et al. 2006), reviews (Rowbotham and Gibson 2011) and projects performed in the last decade discussing potential parameters, criteria and frameworks for EBA as well as related elements (e.g. TTC (Threshold of Toxicological Concern), ADME (absorption, distribution, metabolism, and excretion). Thereby different decision trees have been presented, e.g. decision tree on TTC and internal exposure in Bernauer et al. (2008). Falk-Filipsson and Wallén (2007) present general and specific rules on adaptation, as well as one possible interpretation of the terminology such as limited human exposure, no or non-significant exposure, negligible or unlikely. The project report by Vermeire et al. (2008) provides an extensive discussion of possible information suitable for EBA or indicating testing. Marquart et al. (2012) provides an integrated testing strategy (ITS) developed within the Osiris project.

Further, ECETOC (2020a) has since published Technical report 137 ("Developing the scientific basis for Exposure Based Adaptations (EBA)") which summarized support for, yet shortcomings of, EBA in REACH. However, this work had not proposed a framework to approach applying EBA. Subsequently, a joint workshop was hosted by ECETOC (2020b) for industry and regulators to discuss the viability of EBA. This was summarized in Workshop Report 37 "Online workshop on the scientific feasibility of exposure-based adaptations in the regulatory setting." The principal components of this report were presented at this workshop.

2.2. REGULATIONS

REACH

The REACH guidance document R.5 is considered to be the primary source of information on EBA (ECHA 2011). In this document the framework is outlined including a flow diagram, and a workflow as well as the starting points for EBA justifications. A few situations and examples illustrate and explain the EBA argumentations. The argumentation for EBA referring to Column 2 of REACH Annexes VIII to X is in principle the same as for EBA referring to REACH Annex XI Section 3.2. However, the justification in accordance with REACH Annex XI Section 3.2 has to be developed based on the quantitative exposure estimates derived as part of a chemical safety assessment (CSA), whereas for the qualitative justification under Column 2 of REACH Annexes VIII to X, a weight of evidence approach is expected. The latter can be based on a combination of characteristics of substance hazard profile and emission scenarios, i.e. relevant information on substance properties, use and use conditions, hazard and exposure. In some cases (e.g. Annex VII Section 8.6, 8.7) Column 2 does refer to Annex XI Section 3 that requires quantitative exposure estimates. The Concept of Threshold of Toxicological Concern (TTC) was mentioned in an older version of this guidance, but the reference to TTC and cut-off values has been removed. However, information on the concept of TTC approach is given in the guidance R.7a (ECHA 2017a) with reference to the EFSA/WHO review (EFSA 2016).

In addition, information and criteria on preferred pathways are given and discussed within the toxicokinetic chapter R.7.12 (ECHA 2017b). This includes criteria based

on physico-chemical parameters such as logPow or the molecular weight, or water solubility, vapour pressure and particle diameter.

In the worker exposure assessment guidance R.14 (ECHA 2016), a reference to EBA is given as well. However, negligible exposure in terms of frequency and magnitude is only discussed in the context of closed systems (rigorous containment), and especially for PROC 1 to 3.

In addition, some exposure related information is given in the Regulation (REACH Annex VIII Section 8 Column 2); the appropriate route and duration of testing shall be chosen on the following basis:

- Testing by the dermal route is appropriate if: (1) inhalation of the substance is unlikely; and (2) skin contact in production and/or use is likely; and (3) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin;
- Testing by the inhalation route is appropriate if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size;
- If the frequency and duration of human exposure indicates that a longer term study is appropriate, the sub-chronic toxicity study (90 day) shall be proposed.

Further studies may be required if the route of exposure used in the initial repeated dose study was inappropriate in relation to the expected route of human exposure and route-to-route extrapolation cannot be made, or particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected).

Other regulation/guidance

a) Biocide Product Regulation (BPR)

According to the BPR and guidance (EC 2012; ECHA 2014) for testing repeated dose toxicity only one route of administration is necessary and the oral route is the preferred route. However, in some cases more than one route is necessary to be evaluated.

Some testing can be waived based on exposure consideration (covering primary and secondary exposure under realistic worst-case conditions for all intended uses), i.e. relevant exposure can be excluded in accordance with Section 3 of Annex IV of the Regulation. Testing (core data) for non-threshold effects however cannot be waived (e.g. genotoxicity testing).

If the substance of interest undergoes immediate disintegration, and sufficient information is available for the cleavage products, testing is not necessary.

In addition, some exposure driven threshold values are given in the regulation and guidance indicating where route specific information is necessary or shall be considered:

- The oral route testing is necessary if the active substance may end up in food or feed;
- The dermal route shall be considered with regard to exposure considerations if skin contact is likely and inhalation is unlikely, and dermal absorption is comparable or higher than oral absorption;

- The inhalation route shall be considered if vapour pressure is > 0.01 Pa at 20 °C, or for exposure to aerosols, particles, and droplets if the mass median aerodynamic diameter (MMAD) is < 50 µm.

b) Pesticides Regulation

The pesticide regulation (EC 2009; 2013) also includes provisions for EBA. Guidance documents discuss the concept of negligible exposure (ECPA 2015; Paniagua 2015; SANCO 2015).

The following values should be considered:

- Default maximum residue level (MRL) of 0.01 mg/kg is used for those active substances for which no specific MRL is set out;
- A Vapour Pressure (VP) > 0.01 Pa for volatile substances is a threshold for the requirement of inhalation exposure studies;

For demonstrating negligible exposure an additional and protective "threshold" to the relevant toxicological reference value (e.g. acceptable operator exposure level (AOEL)) is set (not yet defined) or a sufficient safety margin of exposure (at least 1000 on NOAEL of most critical effect) is necessary.

c) Cosmetics Regulation

The Cosmetic regulation 1223/2009 has a completely different risk/benefit balance (ratio) where only the benefit is taken into account (i.e. risk is excluded). Rather, tolerance is considered as the driver for exposure assessment as no PPE are involved. Impurities are also identified and assessed to ensure the safety of the consumer. The TTC approach can be used for some impurities (thresholds depend on the toxicological endpoint). Further, a specific safety factor for vulnerable populations (i.e. babies).

3. DEFINITIONS

A variety of terms in relation to exposure based adaptations is used in Column 2 of Annexes VIII-X and in Annex XI Section 3 of the REACH legislation. To clarify, REACH guidance R.5 provides information on the terminology on adaptation (absence, not significant, no release, etc.). Further discussion and interpretation is given in Falk-Filipsson and Wallén (2007). However, it seems that the terms are still not clearly defined nor harmonized. In the present paper the following definitions/terminology are used:

Exposure based adaptation (EBA):
According to REACH guidance R.5 (ECHA 2011), exposure-based adaptation may be considered in situations where exposure of humans or the environment are absent or so low that the additional effects information will not lead to improvement of risk management. The terminology 'adaptation' comprises all types of modifications of the standard information requirements, including omissions, triggering, replacement or other adaptations.

Relevance of exposure:
According to REACH, data waiving is possible for short-term and sub-chronic repeated-dose toxicity (28d or 90d) or reproductive/developmental toxicity if relevant human exposure can be excluded in accordance with Annex XI Section 3. The latter paragraph considers 'absence of' or 'no significant' exposure. Therefore relevance can be interpreted as an umbrella term.

Absence of exposure:
For risk assessment and EBA purposes, the term 'absence of exposure' should be used only if exposure can be explicitly excluded, i.e. no use, no exposure, or proven no release from the considered end-use e.g. due to containment or if the substance is permanently bound to a matrix. Please note that according to REACH guidance R.5, no-release should not mean zero in the scientific sense, but is to be interpreted as 'practically no release'.

Likelihood:
Based on the discussion in Falk-Filipsson and Wallén (2007), "*the interpretation of 'exposure is unlikely' refers to the probability of exposure to happen, not to the degree of exposure.*" Therefore, this terminology is not related to possible effect concentrations. For risk assessment and EBA purposes, 'unlikely' can be interpreted as exposure is not expected but cannot be fully excluded.

Negligible:
In accordance with SANCO (2015) "'*Negligible' is not equal to zero and is defined in the Oxford English Dictionary as "so small or unimportant as to be not worth considering; insignificant". For risk assessment purposes 'negligible' can be considered to be a level so small that it does not appreciably add to the risk and can safely be ignored.*" Therefore, this terminology is related to possible effect concentrations such as DNEL or TTC, and the expected exposure should be "far below" the level where effects are expected considering the uncertainty of the exposure estimate and toxicological reference value.

Significance:
'Significance' is related to an effect concentration as well, but is not severe as 'negligible'. According to the interpretation of Falk-Filipsson and Wallén (2007) "'*no significant exposure' is defined as a very low level of exposure over a whole lifetime, or a single exposure at a specific occasion. Both the concentration and time is relevant for the determination of no significant exposure.*" For risk

assessment and EBA purposes, no significant exposure can be interpreted as well below the derived appropriate DNEL.

Limited:
'Limited' human exposure is for example mentioned in REACH Annex IX Section 8.6.2 Column 2. According to Falk-Filipsson and Wallén (2007) "*Limited exposure could be considered as exposure below a defined level of exposure, a frequency and/or duration of exposure*." However, 'limited' is very vague, because both exposure on a low as well as on a high level can be regarded as limited. For this reason, without defining the level of exposure, this term should be avoided.

4. DISCUSSION OF CRITERIA, DECISION TREES OR MODELS

The REACH guidance R.5 indicates different approaches (routes) to justify EBA:

- Weight of Evidence (WoE) approach based on Column 2 of REACH Annex VIII-X
- Strictly controlled conditions in accordance with REACH Annex XI 3.2 (b)/(c)
- Quantitative justification in accordance with REACH Annex XI 3.2 (a)

For all routes, toxicological cut-off criteria on one hand and the cut-off criteria for the expected exposure, on the other hand, are necessary to decide on the relevance of exposure.

If a detailed exposure assessment and an appropriate DNEL are available, then a quantitative chemical safety assessment (CSA) to show no significant exposure can be considered a suitable EBA option. Thereby, the ratio of the estimated exposure in the CSA and the derived appropriate DNEL (the risk characterization ratio, or RCR) shows the significance of exposure. In this case, the uncertainty of the derived exposure value and the uncertainty of the toxicological cut-off value should be considered to account for missing toxicological information. If the margin of exposure (MoE) is adequate, i.e. expected worst-case exposure is “well below” the level for any expected effects, exposure can be regarded as not significant, and thus EBA may be justified. Usually a safety factor of 100 (interspecies 10, intraspecies 10) is by default applied to the No-Observed-Adverse-Effect Level (NOAEL) from the animal study. An additional factor might be advisable to address the uncertainty from omitting the study. Similar to the Pesticides Regulation, a margin of exposure / margin of safety of 1000 (on NOAEL of most critical effect) seems to be adequate.

If no appropriate DNEL or no detailed exposure assessment is available, the justification should be based on a weight of evidence (WoE) approach considering hazard and (semi-quantitative) estimations of worst-case exposures based on relevant information on substance properties and typical use conditions. If the expected worst-case exposure is “far below” any expected effects levels, exposure can be regarded as negligible, and thus EBA may be justified.

4.1. TOXICOLOGICAL CUT-OFF CRITERIA (TOXICOLOGICAL REFERENCE VALUES)

If for each exposure route a cut-off level can be determined below which consumer and worker exposure is considered to be negligible or not significant, EBA of repeated dose toxicity studies may be justified. This may be the case if appropriate NOAEL is available for a specific route encompassing all toxic effects and from which an appropriate DNEL can be derived for the route of concern using for example route-to-route extrapolation. In this case, a cut-off level can be deduced from the difference between DNEL and exposure (margin of exposure). However, the uncertainty of exposure estimation and the uncertainty of the DNEL has to be taken into account to be sure that the possibility of health effects can be neglected. For this APROBA-plus (Bokkers et al. 2017), which combines the output from the probabilistic hazard characterization with the probabilistic exposure to rapidly characterize risk and its uncertainty, can be an appropriate tool to analyse and visualise the uncertainty in both hazard and exposure characterization.

4.1.1. Route-to-route extrapolation

According to ECHA (2012a), a DNEL derivation for an endpoint should start from the effects giving the lowest dose and highest concern. However, it may be necessary to derive the correct starting point for a route for which no study was carried out and then a route-to-route extrapolation is necessary.

This approach might be necessary i.e. to derive long-term systemic inhalation/dermal DNELs from the NOAEL of an oral study or vice versa. The ECHA guidance on "How to prepare toxicological summaries in IUCLID and how to derive DNELs" (ECHA 2012b) provides equations on how to perform route-to-route extrapolations. For an extrapolation from inhalation to oral i.e. this would be:

Oral NOAEL = Inhalatory N(L)OAEC/((1/1.15 m^3/kg/d)*($ABS_{oral}/ABS_{inh.}$))

Where,

Oral NOAEL = No observed adverse effect concentration for oral uptake

Inhalatory N(L)OAEC = No (or lowest) observed adverse effect concentration from an inhalation study

ABS_{oral}=oral absorption rate, ABS_{inh} =inhalation absorption rate

Schröder et al. (2016) analysed the uncertainties associated with a route-to-route extrapolation by using a data set of 246 study pairs on 110 chemicals (for oral-to-inhalation) from the Fraunhofer RepDose® database. Based on no/lowest effect levels (NOELs/LOELs) an extrapolation factor of 2.2 (95% confidence interval: 1.2-3.1) was derived for systemic effects in inhalation studies.

On the other hand, according to US-EPA (2002) Inhalation waivers are not granted for active ingredients based solely on low oral toxicity. Toxicity via the inhalation route tends to be more severe than by other routes. Inhaled chemicals by-pass the metabolic protection of the liver (portal circulation). Oral data cannot be used to predict respiratory portal-of-entry effects (e.g. irritation, oedema, cellular transformation, degeneration, and necrosis). The use of route extrapolation in a risk assessment minimizes the true inhalation risk. When calculating inhalation risk, a route-extrapolated MoE will be 6-fold greater than a route-specific MoE when based on rat data. Thus, route extrapolation makes a chemical appear 600% "safer" than it really is. For this reason, route-to-route includes additional uncertainty which should be considered in the MoE for omission of data. This confirms the MoE of 1000.

4.1.2. Threshold of Toxicological Concern (TTC)

If no adequate DNEL can be derived, the concept of Threshold of Toxicological Concern (TTC) may be used as an alternative to judge on negligible exposure and develop justification for EBA. Guidance on the use of TTC is available by EFSA (More et al. 2019).

Route-specific TTC values for non-genotoxic organic compounds are available (see Annex B). According to the structural properties of the compound, the appropriate TTC value has to be selected. It has to be noted, that even the most recent TTC dataset with repeated dose studies on inhalable substances comprises only 296 compounds, either gases or aerosols. This relatively low number limits the applicability of the derived threshold values. In a first approach we therefore

suggest to use the lowest TTC value per route. This could be refined if more specific information on the potency of the substance is available. The TTC for this group can be used when the substance of concern can be considered as a low toxicity compounds (for structural rules see Annex B or the original publication.) This approach results in the use of the following threshold values for non-genotoxic compounds:

Exposure via inhalation:

2 x 10^{-5} ppm/d derived for a class of high toxicity compounds (Tluczkiewicz et al. 2016)

0.05 ppm/d derived for a class of low toxicity compounds (Tluczkiewicz et al. 2016)

Oral exposure:

90 µg/person/day derived for a class of high toxicity compounds, Cramer class 3. Assumes a body weight of 60 kg (Munro et al. 1996).

Route specific TTC values for genotoxic compounds do not exist. Currently, a threshold of 0.15 µg/person/d was proposed for genotoxic compounds via oral application (Kroes et al. 2004) as mentioned by EFSA (More et al. 2019).

Partosch et al. (2015) proposed internal TTC values from merged databases, namely the Munro, ELINCS and FCM database (Annex B). In this approach the nominal NOAEL values were corrected for bioavailability by calculating the absorbed and bioavailable fraction for all compounds with the software ACD Percepta. It is stated that the derived internal TTC levels were based on QSAR prediction of human intestinal absorption as well as physico-chemical properties. As the uncertainty of the calculated values cannot be assessed, the values are not used in this report.

4.2. EXPOSURE CUT-OFF CRITERIA

To exclude potential relevant exposure, different cut-off criteria have been proposed in the literature based on substance inherent properties or product characteristics. Moreover, use specific information may indicate negligible exposure/release. However, a detailed justification for EBA has to be done for each use.

Different (cut-off) criteria presented and discussed in the literature (from guidance, workshops and previous research on EBA) as well as in this report are summarized in Annex C. This list is not exhaustive, a very comprehensive overview and discussion is given in Vermeire et al. (2008). These cut-off criteria from previous literature are briefly presented and discussed in the Section below. In addition, some other (use-independent) exposure cut off criteria were derived to improve the qualitative justification of EBA.

4.2.1. Cut-off criteria for negligible exposure from previous literature

Several substance inherent properties and use parameters could be used as indication that exposure by specific pathway may be negligible, i.e. EBA may be justified using a WoE approach.

General

In general, testing via a certain route is not considered needed if there is no or very limited absorption via that route (Marquart et al. 2012). Generally, log Pow and MW serve as indication for low absorption independent of the exposure route. However, for UVCBs such an approach is of limited applicability as these parameters cannot be derived for complex substances.

According to the REACH guidance for applications with concentrations < 0.02% v/v or < 0.1% w/w no CSA is required. However, if toxic potential is high (e.g. non-threshold effects), it might be necessary to show in a WoE approach that exposure is negligible. As no CSA and thus no detailed exposure assessment is available, this WoE can be based on substance properties such as very low vapour pressure.

Use description

Exposure might be absent if strictly controlled conditions are met. Several PROCs are considered relevant for strictly controlled conditions such as PROC 1, 2 and 3. However, strictly controlled conditions are out of the scope of this project.

PROC 4 implies occasional exposure which does not exclude the possibility completely. However, as mentioned above unlikely exposure does not exclude it either. Therefore, having PROC 4 in the EBA assessment does not necessarily contradict its scope.

PROC 7 and 11 indicate spraying, and inhalation cannot be waived unless aerosols are > 100 µm (see below). For PROC 5, 8a and 17 aerosols can be produced as well.

If a substance is used in PROC 19 'Manual activities involving hand contact' exposure of hands and forearms can be expected (REACH guidance R.12). For this reason, if PROC 19 has to be assessed, relevant dermal exposure is difficult to exclude and the highest dermal exposure are expected in ECETOC TRA v3 for this activity.

Personal protective equipment (PPE) such as gloves are recommended to reduce dermal exposure. However, it might be difficult to show negligible exposure using PPE, especially for professional uses.

Emission to air / exposure by inhalation

Further parameters which maybe applicable indicating negligible uptake by inhalation are Log Koa, and air-blood partitioning.

For (semi)volatile substances evaporation cannot be excluded, but the inhalation exposure maybe negligible or not significant depending on the exposure conditions. However, for substances with very low volatility, i.e very low vapour pressure, inhalation exposure maybe excluded, as long as the substance or product is not sprayed, heated, etc. The question is then about the possibility to determine a cut-off value for vapour pressure below which inhalation exposure is likely to be independent from the exposure situation. In the guidance documents and publications reviewed above, several threshold values have been provided to determine such a value.

In the REACH guidance R.7c (ECHA 2017b) it is stated in the toxicokinetic chapter R.7.12 that highly volatile substances are generally those with a vapour pressure greater than 25 kPa (or a boiling point below 50°C), and substances with low volatility have a vapour pressure of less than 0.5 kPa (or boiling point above 150 °C). This cut off value of less than 500 Pa seems to be not appropriate to exclude

potential of inhalation exposure. The 500 Pa threshold might be of added value for EBA only in combination with other parameters in the use description which also influence the maximum air concentration (such as ventilation, mass transfer rate, etc.).

For waiving Multiple-Exposure Inhalation Toxicity Studies, US-EPA (2002) defines non-volatile active ingredients as having vapour pressures < 0.01 Pa for indoor use, and < 0.1 Pa for outdoor uses at 20 – 30 °C. The value of 0.01 Pa is also stated within the biocidal as well as pesticide regulation above which inhalation exposure is likely.

In ECETOC TRA (ECETOC 2012) model for worker exposure assessment the cut-off for substances with very low vapour pressure is 0.01 Pa, and the max air concentration for this fugacity band is 0.1 ppm. It should be noted that the tool was not designed to indicate negligible exposure but to overestimate the actual exposure. The assessment of the consumer exposure in ECETOC TRA is based on the amount used, and limited to the concentration in air via saturated vapour concentration (SVC).

The German AGBB (AGBB 2015) gives a tiered approach to assess health effects coming from VOC emission of construction materials. The emissions from construction material are assessed using chamber experiments with default loadings and ventilation. The TVOC (sum of all individual volatile substances ≥ 5 µg/m^3 in the retention range of C_6-C_{16}) after 3 days should not exceed 10 mg/m^3 (for carcinogens ≤ 0.01 mg/m^3). After 28 days, the TVOC should be ≤ 1.0 mg/m^3, and the ∑SVOC (sum of all individual semi-volatile substances ≥ 5 µg/m^3 in the retention range of > C_{16}-C_{22}) has to be ≤ 1.0 mg/m^3 (for carcinogens ≤ 0.001 mg/m^3). The latter values seem to be the threshold values indicating negligible exposure for long-term or better medium term exposure whereas the 3 day values are indicating negligible exposure for short-term exposure.

Treatment of solids, pellets, granulates and powders may produce particulate substances in the air which could be inhaled. In addition, during specific activities such as spraying or foaming aerosols can be formed. For particles and aerosols threshold values are discussed in literature, which indicates the presence of inhalable particles. If the use of the substance or the product indicate higher particle sizes, relevant exposure of the particles by inhalation can be excluded. However, if the application, handling or storage will influence the particle size towards smaller particles, this has to be taken into account. For example, for sprays, the generated aerosol size distribution may be altered by evaporation of the solvent.

In the US-EPA (2002) and REACH guidance R.7c (ECHA 2017b) particles < 100 µm have the potential to be inhaled (< 50 µm thoracic, < 15 µm alveolar). According to the biocide regulation there is the possibility of exposure to aerosols, particles or droplets of an inhalable size at MMAD < 50 µm.

Vermeire et al. (2008) takes this criterion that all particles of the original substance should be larger than 100 µm for the consideration of negligible emission of inhalable dust for solids in the form of abrasion-free pellets/ granules. However, there should be pertinent information that handling and storage of the substance does not significantly change the particle size distribution towards smaller particles.

In addition, the Multiple-path Particle Dosimetry Model (MPPD) can be used to calculate the deposition and clearance of monodisperse and polydisperse aerosols in the respiratory tracts of rats and human adults and children.

Dermal exposure

Dermal exposure is considered not relevant when the substance is a gas or a high volatility liquid with short duration of exposure (except when data show relatively high dermal absorption from the vapour or gas phase) (Vermeire et al. 2008). An equation for estimating the evaporation from skin is given in the TGD (EC 2003). As cut-off criterion 10 minutes of continuous exposure with a frequency below 4 times per day is proposed by Vermeire et al. (2008). Dermal exposure might be not relevant if evaporation rate is faster than dermal flux and the dermal uptake is below any expected effects.

Dermal exposure might be also not relevant if the maximum value on skin (immersion) is below any toxic effects. Maximum amount which can stick to the hands by immersion is 6 ml per hand or 12 ml for both hands (HEEG 2008) with 820 cm^2 skin contact area for both hands corresponding to 15 mg/cm^2 per immersion. Important for the daily exposure level is the frequency of immersion per day (shift). In a study of US-EPA (Bryan 1992) the amount of liquid (mineral oil, cooking oil and bath oil) retained on hands have been measured. The values are between 1 mg/cm^2 and 11 mg/cm^2, with the latter value for the viscous mineral oil after immersion. In ECETOC TRA (worker) model based on a maximum loading of 5 mg/cm^2 the highest values of dermal exposure of hands and forearms are 107.14 mg/kg/d (PROC 11 spraying professional) or 141.43 mg/kg/d (PROC 19 hand mixing with intimate contact, industrial and professional). The loading in ECETOC TRA is below the maximum amount which can stick on the hands but in the range of the values given in the US EPA study.

Supporting information for dermal absorption can be achieved by in-vitro studies, or models such as IHSkinPerm (which, however, has limited utility for UVCBs).

Oral exposure

Due to good occupational hygiene, oral exposure by workers is limited to inadvertent or accidental scenarios. Therefore direct oral exposure is negligible.

Unintentional exposure by oral route might be via residues in food, mouthing, dust exposure, aerosol particles which are cleared via gastrointestinal tract.

Indirect exposure of humans via the environment may occur by consumption of food (e.g. fish, crops, meat and milk) and drinking water, inhalation of air and ingestion of soil (ECHA 2017c). Water solubility might be used for max value in surface and drinking water. Max value in fish/plants/meat could be derived using logPow. On the other hand, generic MRL of 0.01 mg/kg is set in the pesticide regulation. In the biocide guidance a trigger value of 4 µg/kg animal (food) is derived based on the EFSA trigger value of 0.1 mg/kg feed. According to the biocide guidance this trigger value should not be used for substances with a potential for non-threshold effects (e.g., genotoxic effects), or for reproductive/developmental/neurotoxic endpoints. These values correspond to a daily human intake of max 0.5 µg/kg bw/d (30 µg/person) using the intake values of the budget method used in the evaluation of food additives (EC 1997). However, the trigger value for this Tolerable Daily Intake (TDI) is three times lower than the oral TTC for Cramer class III substances (90 µg/person or 1.5 µg/kg bw/d).

Oral exposure is reduced by low absorption. Supporting information for absorption can be obtained from in-vitro studies (criteria by Marquart et al. (2012)).

4.2.2. Derivation of (use independent) cut-off criteria

In the chapter above, different threshold values proposed in literature are presented and discussed. Based on these discussions, additional considerations to derive appropriate threshold values for EBA might be helpful especially if no adequate substance specific toxicity value is available, for example, from which vapour pressure level the exposure can be considered as negligible.

Inhalation

Besides a full quantitative risk assessment comparing DNEL for inhalation with exposure estimates (using exposure models, or monitoring data such as workplace measurements), inhalation exposure can also be excluded using a more qualitative assessment in a weight of evidence approach.

Thereby, inhalation exposure can be neglected if relevant air concentration resulting from the substance properties or from the use description can be excluded. The air concentration is limited by the saturated vapour concentration (SVC) using the ideal gas law, which can be maximally achieved by a volatile substance by evaporation at the considered temperature. The approach of SVC is comparable to the approach used for Tier 1 exposure assessment often used for CSA. For a mixture of substances (and UVCBs, if applicable) the partial pressure should be used. In this case it must be secured that the partial pressure will not change over time. For example, if a surface has been treated with an aqueous solution, the partial pressure of the substance in water at this concentration will determine the max air concentration. However, if the water evaporates with time the concentration increases, and thus the partial pressure will increase with time as well. As a worst-case, the nominal/actual vapour pressure and not the partial pressure will define the maximum achievable air concentration. This will not apply to mist, aerosols, fumes, etc.

Using the ideal gas law and the above mentioned max vapour pressure of 0.01 Pa as a threshold value for which exposure by inhalation is likely (US-EPA, pesticides, biocides, ECETOC TRA), this results in following max air concentrations:

VP = 0.01 Pa $\rightarrow c = \frac{n}{V} = \frac{p}{RT} = 4.1\text{E-}06 \frac{\text{mol}}{\text{m}^3}$ at 20 °C

In conclusion, below the vapour pressure of 0.01 Pa at 20 °C, the expected air concentration is definitely below a vapour concentration of 4.1E-6 mol/m^3 at 20 °C (or 0.1 - 10 mg/m^3 depending on the molecular weight[1] of the substance). A concentration below 4.1E-6 mol/m^3 could therefore be considered as a negligible concentration for which in vivo toxicity testing by inhalation is not required.

Indeed, such an assessment ignores the toxicology of the substance. Accepted exposure concentrations (AEC) of substances could be below 4.1E-6 mol/m^3 at 20 °C based on the threshold of 0.01 Pa. If the toxicological information indicates an AEC above this SVC, the inhalation pathway can be neglected if the VP is below 0.01 Pa. However, if no other information is available the TTC for inhalation can be

[1] Using molecular weight of 50 -600 g/mol results in a concentration of 0.2 – 2.5 mg/m^3

converted in a maximal vapour pressure which results in a saturated vapour concentration below this TTC.

If other appropriate toxicological values are available (e.g. OEL, ADI) these values could be used instead of the TTC values to calculate a maximal vapour pressure as well. However, usually these other toxicological values are only reliable if studies on toxicity are available. It seems that in these cases EBA of the data requirement is not necessary, or it can be justified to use the DNEL and apply an appropriate margin of safety.

$$SVC\ \left[\frac{mg}{m3}\right] \leq TTC\left[\frac{mg}{m3}\right]$$

$$\frac{MW \times VP \times 1000}{RT}\left[\frac{mg}{m3}\right] \leq TTC\left[\frac{mg}{m3}\right]$$

$$VP[Pa] \leq \frac{TTC\left[\frac{mg}{m3}\right] \times RT}{MW \times 1000} = \frac{TTC[ppm] \times RT}{V_m[m3/mol] \times 10^6}$$

$$VP\ [Pa] = TTC\ [ppm] \times 0.1\ at\ 20\ °C$$

TTC (low tox) = 0.05 ppm (Tluczkiewicz et al. 2016) → VP = 0.005 Pa at 20 °C
TTC (high tox) = 2 x 10^{-5} ppm (Tluczkiewicz et al. 2016) → VP = 2 x 10^{-6} Pa at 20 °C

Overall, if the vapour pressure is below 2 x 10^{-6} Pa, the expected air concentration will definitely be below the TTC for high toxicity substances, and any inhalation exposure can be neglected. This can be refined for substances where information is available indicating lower toxicity. The TTC for low toxicity substances can be converted in a maximal vapour pressure of 0.005 Pa, which is in a similar range as the generally accepted threshold value for volatility of 0.01 Pa.

The SVC is still a rough worst-case estimation, as it ignores that the substance has to be distributed from the surface into the inhalable air volume, and this mass transfer depends on the model used, the air flow over the surface and the diffusivity of the substance in air. The predicted mass transfer coefficient for a flat surface is typically in the range of 2 to 16 m/h (Delmaar 2010). The time to get the saturated air concentration even for a relatively small room volume (cloud around the source) can be very significant as shown in the following figure, i.e. the variability is not very high for the 8h-TWA or 24h-TWA, but if the use indicates shorter exposure duration or shorter emission duration, this could have an influence on the maximal resulting dose. Already after 15 min of emission, the expected concentration in this small cloud around the source will be about 25% of the SVC using the default mass transfer coefficient of 10 m/h. Moreover, the concentration will be reduced by ventilation into the far field or outside of the room. In conclusion, the SVC will overestimate the max inhalable dose, and thus will be an appropriate worst-case consideration to exclude relevant inhalation exposure.

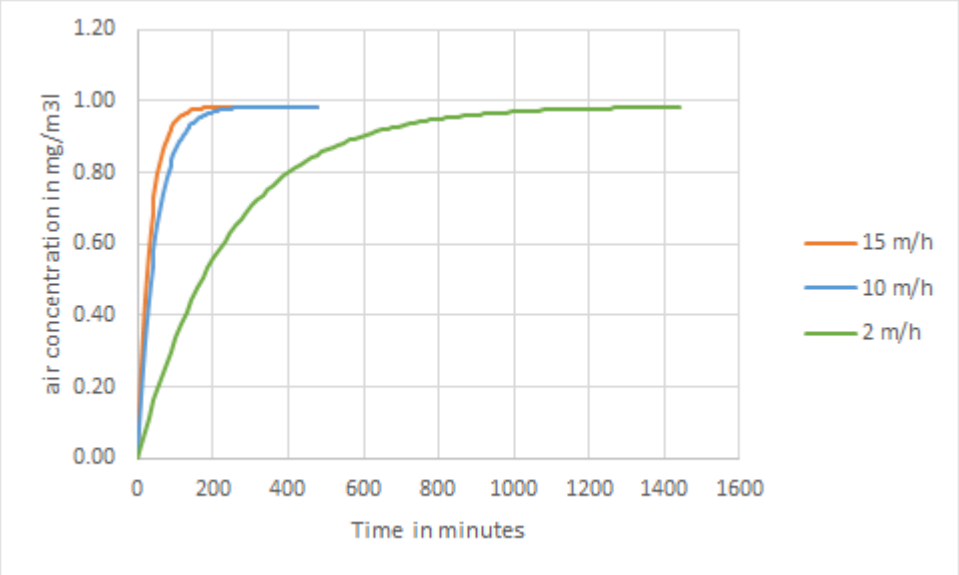

Figure 1 ConsExpo calculation of the time for reaching SVC (0.98 mg/m^3) in dependence of the mass transfer rate (substance with 0.01 Pa, 240 g/mol, surface 1 m^2, room volume 8 m^3, 20 °C, no ventilation)

The SVC approach based on the vapour pressure (ideal gas law) will not apply to mist, aerosols, fumes, etc. Moreover, if the substance or product will be substantially heated during use, or used at higher temperatures, or if the substance will get in contact with high temperature surfaces, the vapour pressure increases exponentially, resulting in a higher evaporation rate. As the surrounding environment may have lower temperatures, the evaporated substance will condensate or deposit on surfaces or particles (dust). In this case, the temperature in the room (or sub-room above the source) determines the SVC, and thus the inhalable dose of the vapour, but additionally the uptake by particles has to be considered in the weight of evidence approach justifying negligible exposure.

If no exact vapour pressure for the product is available, chamber experiments similar to the AGBB scheme may be used (loading, ventilation adapted to the intended use). The resulting cut-off criteria of the AGBB scheme (see chapter 4.2.1) are similar to the SVC values estimated using the default of 0.01 Pa.

Furthermore, the internal exposure can be estimated using Koa and an estimation of blood-air partitioning. However, as long as no internal TTC is available, it will be difficult to decide on a threshold value for negligible internal exposure by inhalation.

Dermal

As for the inhalation route, instead of a full quantitative risk assessment comparing appropriate DNEL for dermal exposure with appropriate exposure estimates (using exposure models, or monitoring data such as workplace measurements), relevant dermal exposure can also be excluded using a more qualitative assessment in a WoE approach. Thereby, dermal exposure can be neglected if relevant skin contact resulting from the substance inherent properties or from the use description can be excluded.

For evaporating substances the calculation of the evaporation time from the skin will determine if the inhalation is the primary route of exposure or dermal. If full

evaporation is expected based on substance inherent properties within a relatively short time, dermal exposure can be neglected.

For the evaporation from skin Vermeire et al. (2008) states that “Dermal exposure is not relevant when the substance is a gas or a high volatility liquid with short duration of exposure (except when data show relatively high dermal absorption from the vapour or gas phase). The TGD contains an equation to calculate evaporation from the skin. A criterion could be:

- full evaporation of high levels of contamination can be expected in a matter of minutes (say < 10 minutes), and
- duration of continuous exposure is no longer than 10 minutes and frequency is not greater than four times per day.

With the equation provided in the TGD and exposure estimates for high exposure tasks, this can be further specified towards the vapour pressure of the substance that will ensure sufficiently quick full evaporation.”

Calculated evaporation times are given in the TGD (EC 2003). Thereby the evaporation time for extensive contact (5 mg of substance) is < 10 min at vapour pressures about > 1000 Pa at 20 °C. However, as mentioned by Vermeire et al. (2008), this is not adequate if the substance show a relatively high dermal absorption potential. Therefore, the evaporation rate should additionally be significantly faster than the dermal flux (predicted using for example IHSkinPerm) to neglect significant dermal exposure.

For non-evaporating substances or slowly evaporating substances, dermal exposure cannot be excluded. Thereby, the dermal exposure is limited by the maximum amount of substance which can adhere on the skin. The estimated maximum amount on hands by immersion or by contact to a treated surface (transfer) can thus be used as a surrogate for the maximal dermal exposure. This could be refined if the use description indicates that other parts such as lower arms, or body are exposed too. These estimated maximal exposure levels could be compared to an appropriate TTC. Or similarly to inhalation exposure, a concentration on skin can be calculated based on the TTC assuming 100% absorption as a worst-case. If this dermal exposure is below the TTC, exposure can be neglected. The maximum amount of substance which can adhere on the skin is 12 ml for both hands corresponds to 200 mg/kg/d using a body weight of 60 kg. This value is higher than the estimated maximal values by ECETOC TRA. For comparison the proposed dermal TTC for Cramer class III substances is 2.5 µg/kg/d (Marquart et al. 2012; Van de Bovenkamp and Buist 2010). Therefore, assuming 100% absorption as a worst-case, the fraction of the substance in the product on the skin should not exceed 0.001%.

However, the internal exposure is limited by dermal absorption rate. If this can be considered, the TTC for dermal exposure should be based on internal exposure values. As mentioned above, some approaches exist to derive internal TTC values. However, due to the uncertainty such values are not used in this report.

Oral

As a threshold value for negligible exposure by oral uptake the TTC (as a worst-case the value of Cramer class III) can be used, i.e., 90 µg/person. However, this value is not applicable for non-threshold effects.

Based on this TTC and the generally accepted water consumption of 2 Litres per person on day, a maximal allowable residue level of 45 µg/L in drinking water can

be estimated. As the maximal content in drinking water (and surface water) is limited by the water solubility of the substances, all substances with water solubility below this concentration indicate negligible exposure by this pathway. A similar approach can also be used to estimate maximal possible values in fish/plants/meat using the log Pow of the substance.

The approach could be refined if ADI values for the substance exist. However, if appropriate ADI exist, data on repeated oral toxicity data are available in most cases.

5. FRAMEWORK ON EXPOSURE BASED ADAPTATION

The starting point for developing the EBA framework in this study was the original EBA framework presented in REACH guidance R.5 including flow diagram, use description criteria, info checklists (ECHA 2011). To support the decision on whether EBA of an animal study may be justified, it is proposed to use the cut-off criteria described in Chapter 4 of this report. In addition, the flow diagram for decision on the appropriate route of justification (approach) will complement the flow diagram in guidance R.5.

STEP 1: Collection and assessment of available information
Substance description and properties
Use description
Exposure monitoring data (where available)

STEP 2: Select an approach for justification (route of justification according to guidance R.5)

In this step the approach for justification will be selected (see Figure 2). A selection will be necessary for each end-use.

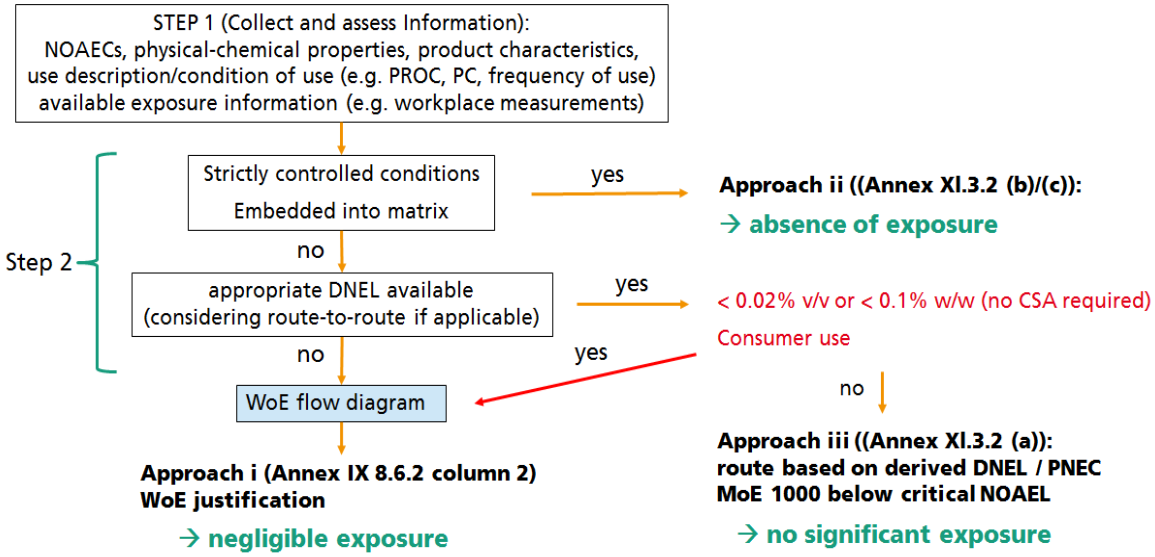

Figure 2 Flow diagram for selection of appropriate approach for justification (route of justification according to guidance R.5)

Approach i: Weight of evidence (WoE) approach based on Column 2 of REACH Annex VIII to X
This route applies to substances where registered uses are not solely strictly controlled conditions or inclusion into article matrix, and no adequate DNEL exists (thus quantitative approach not possible).

Approach ii: Justification in accordance with REACH Annex XI. 3.2 (b) / (c)
This route applies to substances with uses under strictly controlled conditions or inclusion into an article. This route is out of the scope of this project.
The burden of proof then condenses to the necessity to demonstrate the strictly controlled conditions as implemented at the site or to justify how the substance is bound into an article matrix.

Approach iii: Quantitative justification in accordance with REACH Annex XI 3.2 (a)
This route applies to substances with uses for which a quantitative justification of the exposure based adaptation is applicable (i.e. comparison with a DNEL).
This is only possible if there is a DNEL for the exposure route to be considered, an adequate exposure assessment (CSA) resulting in an acceptable margin of exposure (MoE) or if the uncertainty analysis of the exposure assessment results in exposure values sufficiently lower than the DNEL.

Note: Demonstrating negligible exposure for consumer uses may be challenging, especially if the DNEL(s) are very low. However, it may be still possible to justify EBA or a specific exposure route for testing based on the intrinsic physical-chemical properties (vapour pressure). In this case the assessor should choose to go to the WoE route (approach i in Figure 2). It is also important to note that when adapting an information requirement using the WoE approach special consideration should be given to ensure that the prospective study outcome is adequate for both hazard identification (C&L) and risk characterization purposes. In the example of determining the most appropriate administration route for animal testing having regard to the likely route of human exposure the objective would be to try find an optimum administration route that significantly contributes to systemic dose yet enables reliable DNEL derivation without the need for additional adjustment factors (e.g. for route-to-route extrapolation).

STEP 3: Develop Justification

The justification is irrespective of the type of approach selected. For the WoE approach, the flow diagram in Figure 3 can be used to facilitate argumentation of the adjustments. A justification needs to be built for each use.

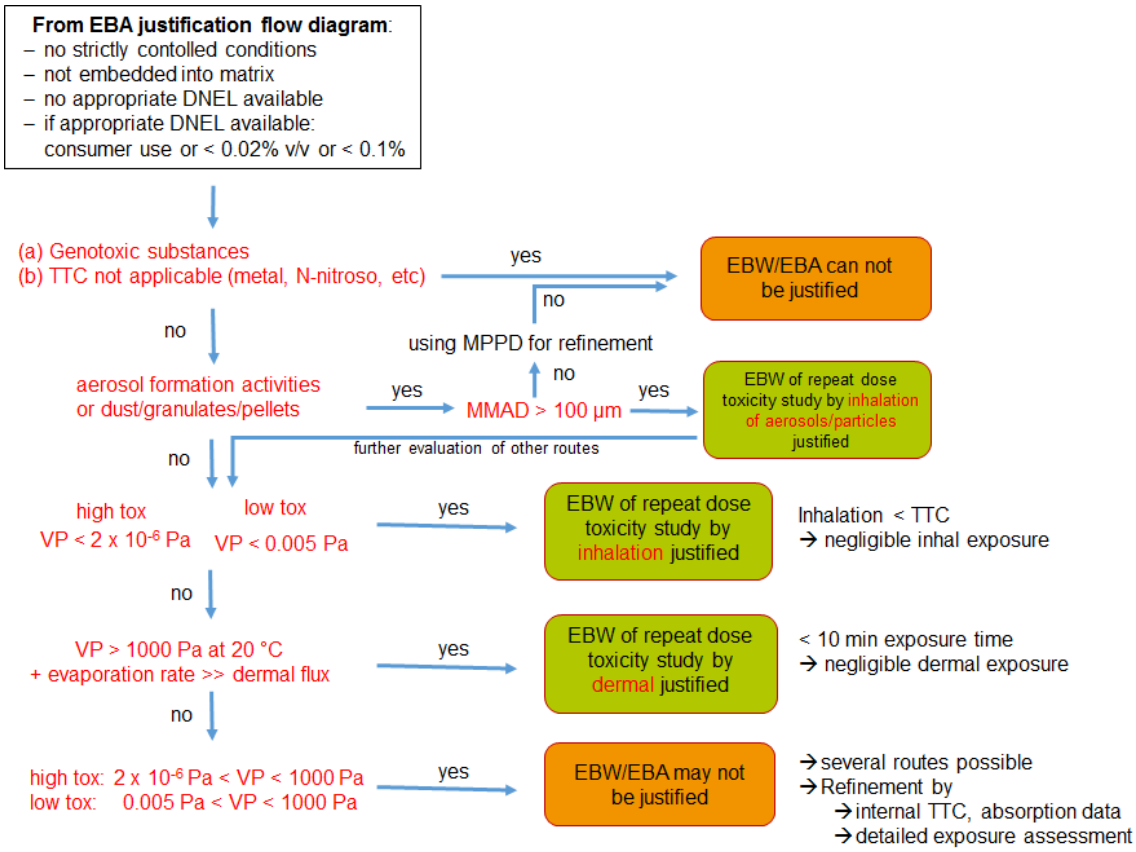

Figure 3 Flow diagram for criteria used for justification based on weight of evidence

STEP 4: Conclusion (Illustrate Justification)

The justification needs to be summarized similarly to the examples in REACH guidance R.5 (ECHA 2011).

Box 2: Examples for illustration of justified and not justified EBA

Type of study to be adapted (a)	applied rule for adaptation	Substance properties or operational conditions.	Argumentation
Short-term repeated dose toxicity study (28 days) (Annex VIII 8.6.1)	Annex VIII 8.6.1 column 2, with reference to Annex XI section 3	The substance is manufactured and used under rigorous containment and "no release" conditions apply over the entire lifecycle.	Rigorous containment and procedural and control technologies and "no release" conditions, as well as qualitative and quantitative risk considerations are exemplified in Appendix 1 to this document.
Sub-chronic toxicity study (90 days) (Annex IX 8.6.2)	Annex IX 8.6.2 column 2	The substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure.	Due to the physicochemical properties, exposure by inhalation is absent (data on volatility/granulometry). The formation of dusts/aerosols is not significant due to the specific operational conditions. Toxicological data on absorption. Robust information on negligible exposure available.
Sub-chronic toxicity study (90 days) (Annex IX 8.6.2) and information on adsorption/desorption depending on the results of the study required on Annex VIII (Annex IX 9.3.3)	**Annex XI 3 b**	The substance is manufactured and used under rigorous containment and "no release" conditions apply over the entire lifecycle.	Rigorous containment and procedural and control technologies and "no release" conditions, as well as qualitative and quantitative risk considerations are exemplified in Appendix 1 to this document.
Type of study <u>not</u> to be adapted (b)	**applied rule for adaptation**	**Substance properties or operational conditions.**	**Argumentation**
Short-term repeated dose toxicity study (28 days) (Annex VIII 8.6.1)	**Annex XI 3 a-c**	Substance is used in consumer products.	When a substance is used in consumer products, then relevant human exposure is difficult to exclude.
Short-term repeated dose toxicity study (28 days) (Annex VIII 8.6.1)	**Annex XI 3 c**	Substance is incorporated in article during the life cycle stage relevant to consumers.	While it may be possible to demonstrate that the substance is not released during the service life stage (e.g batteries or compressor fluids in refrigerators), it is difficult to exclude releases during the waste life stage. This is due to the fact that i) recollection rate of end of service life articles from consumers is usually not higher than..... % *(to be filled in)* and ii) that the matrix or the rigorous containment may be destroyed by milling and thermal treatment processes.
Sub-chronic toxicity study (90 days) (Annex IX 8.6.2)	Annex IX 8.6.2 column 2	Repeated exposure is likely but exposure levels are uncertain.	In general when repeated human exposure to a substance can be expected, adaptation is not a possibility, unless it can be demonstrated in a quantitative justification that risk is negligible.

Figure 4 Examples how to illustrate and justify EBA; taken from REACH guidance R.5 (ECHA 2011)

6. CONCLUSION AND RECOMMENDATION FOR FUTURE WORK

A proper knowledge of the intrinsic properties of a chemical substance is a prerequisite to perform its risk assessment and identify the related risk management options. Exposure-based adaptation (EBA) is an important tool to characterise exposure via possible routes according to the use pattern and to avoid unnecessary animal testing. It should be considered in situations where direct exposure to humans or via the environment is absent or so low that additional effects information will not lead to improvement of already defined risk management measures (if any).

In this project, information and criteria for EBA have been summarized considering provisions in existing regulations, compilation of information from several workshops, reviews of pertinent literature and projects performed in the last decade discussing potential parameters, criteria and frameworks for EBA as well as related elements (e.g. TTC, ADME). As a preliminary finding, the literature search indicated that better definitions of the terminology used within the context of EBA was necessary, including terms such as relevance, absence, likeliness, significance, and limited.

The EBA can be based on toxicological threshold criteria as well as exposure driven threshold criteria. The toxicological threshold can be based on NOAEL (if deemed to be reliable using route-to-route extrapolation). In this case, an EBA can be justified when the risk assessment results in a safety margin of exposure (MoE) considered as acceptable.

If there is no NOAEL for the considered exposure route, it can be referred to the threshold of toxicological concern (TTC) to show negligible exposure. Bioavailability should then also be considered, with the limitation that there is currently no adequate internal TTC values.

In this project, the TTC values for inhalation exposure have been converted to a vapour pressure which can be used as a use-independent exposure cut-off value. The vapour pressure of the substance indicates also the cases where dermal exposure becomes less relevant than inhalation exposure due to high evaporation rates. For oral exposure some preliminary derivations, not integrated in the framework, have been based on oral TTC and drinking water consumption.

Based on these findings, additional flow diagrams have been developed supporting the flow diagram already available in REACH guidance R.5. These flow diagrams can serve as decision trees for selecting the approach for building the EBA justification; they also integrate quantitative metric values for the weight of evidence approach.

UVCB petroleum substances were considered for EBA evaluation. However, it was determined that EBA is not meaningfully applicable due the compositional complexity of the substances and to Uses of these substances resulting in inevitable exposure

Overall, this framework is intended to improve the quality of justifications for EBA and should contribute to a better acceptance of these justifications for the purposes of REACH CSAs and the resulting identification of risk management measures.

Future research is needed to refine some elements of the framework, e.g. to be able to use internal TTC or cut-off values for oral exposure.

- Based on internal TTC, negligible exposure could be justified due to negligible absorption and bioavailability (to be used in case of oral exposure and particularly in case of dermal exposure). However, adequate internal TTC are not available so far.
- Derivation of threshold criteria for oral exposure based on water solubility (intake of drinking water) or residue levels in food. In this context, maximum residue levels in food or migration limits for food contact material along with exposure estimation method for food ingredients (e.g. budget method, EFSA database on food consumption, etc.) may be helpful.

7. ACRONYMS AND ABBREVIATIONS

ADI	Acceptable Daily Intake
ADME	Absorption, distribution, metabolism and elimination (properties)
AEC	Accepted Exposure Concentration
AOEL	Acceptable Operator Exposure Level
CSA	Chemical Safety Assessment
DNEL	Derived No Effect Level
EBA	Exposure Based Adaptation (see ECHA guidance R.5)
logPow	Partitioning coefficient between octanol and water
MMAD	Mass Median Aerodynamic Diameter
MoE	Margin of exposure
MPPD	Multiple-Path Particle Dosimetry Model
MRL	Maximum Residue Level
MW	Molecular Weight
NOAEL	No Observed Adverse Effect Level
PC	Product Category (see ECHA guidance R.12)
PPE	Personal Protective Equipment
PROC	Process Category (see ECHA guidance R.12)
TGD	Technical Guidance Document
TRA	Targeted Risk Assessment, a Tier 1 exposure model developed by ECETOC. For the purpose of this document v3 was used. TRA has since been updated to v3.2.
TTC	Threshold of Toxicological Concern
UVCB	Unknown or Variable composition, Complex reaction products or Biological materials.
VP	Vapour Pressure
WoE	Weight of Evidence
WS	Water Solubility

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ANNEX A: LITERATURE SEARCH

Search was done in PubMed and Scopus, as well as in Web (google). Search terms were:

- exposure
- exposure based

in combination with:

- waiving
- trigger
- adaptation
- TTC (Threshold of Toxicological Concern)
- negligible

The search resulted overall in about 200 hits.
This literature was then limited within Endnote by the search terms ‘reproduct*’ or ‘repeated’ in the title, abstract or within the document. This limitation resulted in about 30-40 relevant publications or project reports in addition to regulations and guidance. Other publications focus more on the environmental exposure. This set of documents have been supplemented by already available information on TTC, and documentation on exposure models.

This search (PubMed and GoogleScholar) was repeated in 2024 with no additional relevant literature found.

ANNEX B: TTC VALUE OVERVIEW

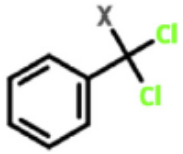
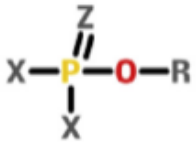
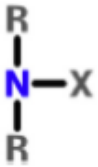
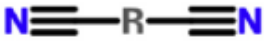
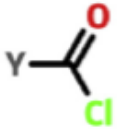
Table 1 Inhalation threshold values

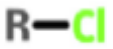
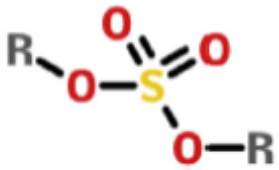
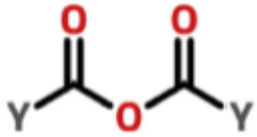
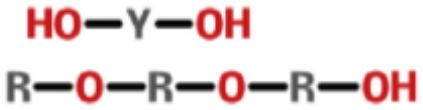
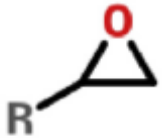
Type	Classification	N	Threshold value#	Unit	Threshold (µg/kg bw/d)	Threshold (µg/person*/d)	Description	Reference
Systemic	Cramer class 1	92	16.4	µg/bw /d		980	Includes some inorganic compounds	Carthew et al. (2009)
	Cramer class 3		2.8	µg/kg bw /d		170		
Local	Cramer class 1	92	2.1	µg/kg lung tissue /d		200		
	Cramer class 3		0.73	µg/kg lung tissue /d		67		
General	Low Tox	81	0.05	ppm/d		4260	New structural and MoA classification based on NOECs for 296 cmpds, includes the organic compounds from Carthews et al. 2009	Tluczkiewicz et al. (2016)
	High Tox	155	2×10^{-5}	ppm/d		2		
Systemic	Cramer class 1	83	0.07	mmol/d			OELS- 8-h threshold limit values—Time-Weighted Average for 280 organic Substances, Cramer classification applied, systemically acting non carcinogenic	Chebekoue and Krishnan (2017)
	Cramer class 2	12	0.004	mmol/d				
	Cramer class 3	185	0.003	mmol/d				

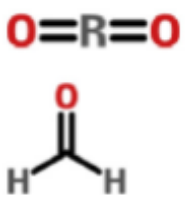
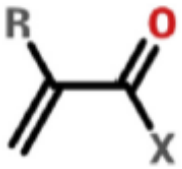
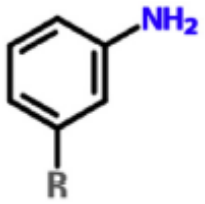
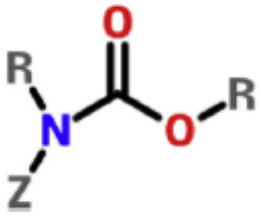
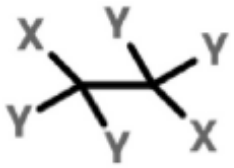
*assumes body weight of 60 kg
based on 5^{th} percentiles

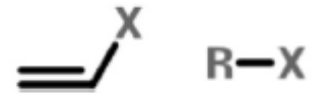
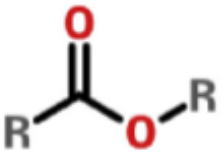
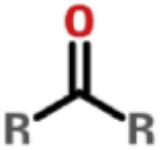
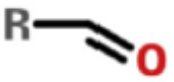
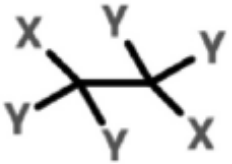
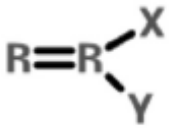
Table 2 Structural rules discriminating between high and low toxic compounds are shown (taken from Tluczkiewicz et al. (2016))

Overview on the structural rules for identifying toxic (T) and lower toxic (L) compounds (9 L- and 19 T-groups); rules being identical to Schüürmann et al. (2016) are indicated (*).

SF	Name	Structure	
T2*	Benzyl chlorides		X=H or Cl
T3	(Thio)phosphoric acid esters		Z=O or S X=O, N, S, Cl
T4	Aliphatic sec. and tert. amines, cyclic amines		R=C (aliphatic) X=H, C (aliphatic)
T6*	Nitriles		R=C (aliphatic)
T8*	Carbonyl chlorides		Y=O, Cl, C (aliphatic)
T9	Cyclic amides (Lactams)		Z=H, C (aliphatic) R=C (aliphatic)

T11	Cyclic haloalkanes		R=C (aliphatic, cyclic)
T12*	Aliphatic sulfates		R=C (aliphatic)
T13*	Anhydrides		Y=N, C (aliphatic)
T14	Aromatic alcohols, cyclic alcohols, aliphatic alcohols with C–C triple bond		R=C (aliphatic) Y=C (aliphatic or aromatic)
T15	Glycol ether (SU* = 2)		R=C (aliphatic)
TR1	Epoxides		R=H, C (aliphatic, halogenide substituents possible), O (aliphatic ether)
TR2	Isocyanates		R=C (aliphatic)

SF	Name	Structure	
TR4	Dialdehydes, formaldehyde		R=C (aliphatic)
TR5	α, β carbonyl compounds, acrylates		R=S, C (aliphatic) or H X=OR
TR7	Aromatic amines		R=NO_2, CH_3, Cl, H
TR9	Carbamates		R=C (aliphatic) Z=H or C
TR11	Non-fluorine haloalkanes, vic. non-fluorines, allyl/vinyl haloalkenes		X=Cl, Br Y=H, Cl, O, C (aliphatic)

			
L1	Aliphatic ether, cyclic alkane, Glycol ether (SU* = 1)		R=C (aliphatic) Y = Alcohol or ester group
L2	Aliphatic esters		R=C (aliphatic)
L3	Aliphatic ketones		R=C (aliphatic)
LR4	Aliphatic monoaldehydes		R=H, C (aliphatic)
LR5	Fluorine alkanes, geminal alkenes, vic. fluorines		X=F Y=F or Cl R=H, C (aliphatic)
			
			
L6	Aliphatic alcohols		X=OH, H R=C (aliphatic)

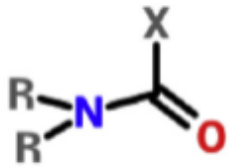
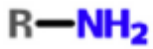
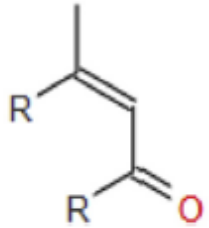
SF	Name	Structure	
L7	Amides		X=H, C (aliphatic, chain) R=C (aliphatic)
L8	Aliphatic prim. amines		R=C (aliphatic)
LR9	Alkylated α, β carbonyl compounds		R=C (aliphatic) or H

Table 3 Different TTC values for different pathways (taken from Marquart et al. (2012)):

Table 2
Proposed thresholds of toxicological concern to be used with the decision tree on Exposure Based Waiving for direct human exposure.

Compounds	Oral TTC (μg/day)[a]	Inhalation TTC general population (μg/day)[b]	Inhalation TTC workers (μg/day)[b]	Dermal TTC (μg/kg bw/day)[c]
Non essential metals, metal containing compounds, proteins, polyhalogenated-dibenzodioxins and related compounds	(excluded from approach)			
Aflatoxin-like, azoxy or *N*-nitroso-compounds	(excluded from approach)			
Substances suspected to be genotoxic carcinogens	0.15	–	–	0.0025
Organophosphates	18	–	–	0.3
Cramer structural class III	90	3	200	2.5
Cramer structural class II	540	–	–	9
Cramer structural class I	1800	200	480	30

– = Not determined.
[a] Kroes et al. (2004).
[b] Escher et al. (2010).
[c] Van de Bovenkamp and Buist (2010).

Table 4 Internal TTC values from (Partosch et al. 2015):

Table 3 Internal TTC values (µg/kg bw/d) derived from the merged databases (Munro, ELINCS, FCM)

Origin of TTC value	Internal TTC value for Cramer class I ($n = 287$) in µg/kg bw per day	Internal TTC value for Cramer class II/III ($n = 1,289$) in µg/kg bw per day
Based on 5th percentile of the distribution of the NOAELs (corrected for bioavailability)	6.9 3.8–11.5	0.1 0.08–0.14
Based on 10th percentile of the distribution of the NOAELs (corrected for bioavailability)	38.6 31.5–40.5	1.5 1.2–1.9

The external oral NOAEL were corrected for bioavailability, the 5th and 10th percentiles of the distribution were taken divided by the default uncertainty factor of 25. Using Monte Carlo simulation, 90 % confidence intervals were computed. Distributions of bioavailability and of time extrapolation factors were taken from references (Reynolds et al. 2009; Table 2.13 in Schneider et al. 2005)

ANNEX C: OVERVIEW OF AVAILABLE CRITERIA PRESENTED IN GUIDANCE, WORKSHOPS, OR RESEARCH

Table C1 General criteria (not route specific) presented in guidance, workshops, or research

Criteria	application	Reference	Assessment if robust for EBA
Wide spectrum of uses Consumer use	Difficult to justify EBA	ECHA (2011)	According to guidance R5 Box 2 "When a substance is used in consumer products, then relevant human exposure is difficult to exclude"
Strictly controlled conditions No dispersive use / no consumer exposure		ECHA (2011)	
logPow			as indication for low absorption independent of the exposure route
MW			as indication for low absorption independent of the exposure route

Table C2 Criteria for **inhalation** exposure route presented in guidance, workshops, or research

Criteria	application	Reference	Assessment if robust for EBA
Severe Irritation and Corrosivity pH <2 or >11.5	Waiver for multiple exposure inhalation studies	US-EPA (2002)	Waiver not possible for slight to moderate irritants
Low volatility VP < 0.01 Pa indoor use VP < 0.1 Pa outdoor use at 20-30 °C	Waiver for multiple exposure inhalation studies	US-EPA (2002)	
Large aerosols particle size > 100 µm (99% of the particles) resistant to attrition	Waiver for multiple exposure inhalation studies	US-EPA (2002)	

Criteria	application	Reference	Assessment if robust for EBA
Toxicity cat 4 and MOE > 1000	Waiver for multiple exposure inhalation studies	US-EPA (2002)	
VP > 0.01 Pa at 20 °C	Testing acute toxicity by inhalation Testing inhalative repeated dose shall be considered	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	This value represents more at which VP a study is necessary as exposure is likely (additionally to oral), and not below exposure is negligible VP< 0.01 Pa corresponds to 0.1 - 10 mg/m^3 based on the saturated vapour concentration (SVC) (see below 3.4.1)
MMAD < 50 µm (additionally at acute toxicity "significant proportion (e.g. 1 % on a weight basis)")	Testing acute toxicity by inhalation Testing inhalative repeated dose shall be considered	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	Relevant for aerosols and particulate inhalation exposure
VP > 0.01 Pa at 20 °C route-specific kinetic data	Testing acute toxicity by inhalation; Head/nose only Short term shall be performed by inhalation exposure	Regulation on plant protection products (EC 2013)	
MMAD < 50 µm Significant proportion (> 1 % on a weight basis)	Testing acute toxicity by inhalation Head/nose only	Regulation on plant protection products (EC 2013)	
included in products that are powders or are applied by spraying	Testing acute toxicity by inhalation Head/nose only	Regulation on plant protection products (EC 2013)	
Additional safety factor to AOEL (not yet defined) MoE of 1000 (to NOAEL)	Negligible non-dietary exposure	Regulation on MRL (EC 2005) Draft guidance on negligible exposure (SANCO 2015)	This is not a waiver for testing.

Criteria	application	Reference	Assessment if robust for EBA
Highly volatile: VP > 25000 Pa or boiling point < 50 °C low volatility: VP < 500 Pa Or boiling point > 150 °C	General guide, available for inhalation as vapour	Guidance R7.12 Toxicokinetics (ECHA 2017b)	
Particle size < 100 µm inhalable < 50 µm thoracic < 15 µm alveolar	Indicating general deposition pattern	Guidance R7.12 Toxicokinetics (ECHA 2017b)	
logPow (between -1 and 4) logPow > 4	Absorption by passive diffusion Micellular solubilization	Guidance R7.12 Toxicokinetics (ECHA 2017b)	
< 15 µm	Default Inhalation cut-off criteria	ConsExpo	
VP < 2 x 10^{-6} Pa (VP < 0.005 Pa for low tox chemicals)	Negligible exposure	This project	Value was calculated based on SVC and TTC for high tox chemicals. For uncertainties see chapter 4.2.2 For mixtures the partial pressure is relevant. Not applicable to genotoxic substances. Value is mostly independent on use; For scenarios with higher process temperatures, the SVC has to be adjusted.

Table C3 Criteria for exposure route **dermal** presented in guidance, workshops, or research

Criteria	application	Reference	Assessment if robust for EBA
- Inhalation of the substance is unlikely, - skin contact is likely - physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin, or - the results of an in vitro dermal	Testing acute toxicity by dermal is necessary	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	

Criteria	application	Reference	Assessment if robust for EBA
penetration study (OECD 428) demonstrate high dermal absorption and bioavailability			
dermal absorption is comparable or higher than oral absorption	Testing dermal repeated dose shall be considered	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	
acute dermal toxicity < oral toxicity	Testing dermal repeated dose shall be considered	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	
case by case basis, unless the active substance is a severe irritant	Short-term dermal studies shall be considered	Regulation on plant protection products (EC 2013)	
Additional safety factor to AOEL (not yet defined) MoE of 1000 (to NOAEL)	Negligible non-dietary exposure	Regulation on MRL (EC 2005) Draft guidance on negligible exposure (SANCO 2015)	This is not a waiver for testing.
Full evaporation < 10 min Exposure < 10 min consecutively and frequency < 4 times per day	Dermal exposure not relevant, except if high absorption	Vermeire et al. (2008)	Evaporation rate of mixtures? to compare additionally evaporation rate with dermal flux

Table C4 Criteria for exposure route **oral** presented in guidance, workshops, or research

Criteria	application	Reference	Assessment if robust for EBA
Gas or highly volatile	Waiver for acute oral study	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	No specific value given. Gas is a substance with boiling point < 20 °C
end-up in food or feed	Testing oral repeated dose is necessary	Biocidal product regulation 528/2012 (EC 2012) Guidance on BPR Volume III Part A (ECHA 2014)	For example if used in PT3, PT4, PT5, or PT18 unless it can be shown that residues are negligible
MRL < 0.01 mg/kg (or LOQ)	Negligible dietary exposure	Regulation on MRL (EC 2005) Draft guidance on negligible exposure (SANCO 2015)	This is not a waiver for testing.
Total daily intake based on the PEC	Indirect exposure of humans	Guidance on BPR Volume III Part B/C (ECHA 2017c)	Consumption of food and drinking water, (inhalation of air) and ingestion of soil

Criteria	application	Reference	Assessment if robust for EBA
4 µg/kg residue in animal	Threshold value for negligible dietary exposure	Biocide guidance	corresponding to EFSA trigger value of 0.1 mg per kg feed which leads to TMDI of 293 µg/person (or 5 µg/kg/d) g/kg in food not applicable for substances with non-threshold effects or reproductive / developmental / neurotoxic
Uses with food contact (e.g. PT3, PT4, PT5, etc.)	Estimating dietary risk	Guidance on BPR Volume III Part B/C (ECHA 2017c)	Tiered approach using default trigger of 4µg/kg in food
Water solubility < 45 µg/L	Negligible exposure by drinking water	This project	Based on the oral TTC of 90 µg/person in combination with daily consumption of 2 Litres drinking water.
Water solubility < 0.075 µg/L for genotoxic compounds	Negligible exposure by drinking water	This project	Based on the oral TTC of 0.15 µg/person for genotoxic compounds
< 0.1 µg/L	Negligible exposure by drinking water	BPR and Pesticide regulation Drinking water guideline	Cut-off value for allowed concentration in drinking water

ANNEX D: REPORTS OF RELATED EBA WORK

Significant portions of this report were presented at the October 2020 ECETOC Workshop "Online workshop on the scientific feasibility of exposure-based adaptations in the regulatory setting" and summarised in Workshop Report no.37 (ECETOC 2020). Further, ECETOC established a task force to review and recommend improvements to the EU's REACH legislation regarding minimal or no human or environmental exposure. In May 2021, the task force published Technical Report no.137 "Developing the scientific basis for Exposure Based Adaptations (EBA)" (ECETOC 2021). One of the recommendations of TR 137 is to develop for human health a "more exposure-driven hazard generations framework as already implemented for environmental endpoints." We find our report "Framework on Exposure-Based Adaptation of (human health) REACH hazard information requirements" succeeds in describing such.

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