Developing the scientific basis for Exposure Based Adaptations (EBA)

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EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

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Table of Contents

Introduction

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation was adopted by the European Union (EU) to ensure chemicals manufactured or imported into the EU are safe for human health and the environment when used as intended (European Commission, 2006). The manufacturer or importer is responsible for compiling a registration dossier that outlines the physicochemical, environmental fate, ecotoxicological, and toxicological properties of the substance. Depending on the amount of substance manufactured or imported, a minimum dataset is required in the dossier to enable the safety assessment. The REACH regulations also allow a manufacturer or importer to adapt or modify these data requirements based on the exposure potential of the substance. These adaptations are known as Exposure Based Adaptations ('EBA'). The EBAs are intended to be used when human and environmental exposures are low such that there is a low probability that additional data will improve the ability to identify and manage risk. Exposure forms a cornerstone to risk assessments conducted under REACH, however EBAs have not been deployed in a consistent manner. The inconsistent legislative provisions and lack of guidance has led to a minimal use of EBA. This represents a missed opportunity to develop a science-based, sound and coherent EBA approach and in subsequentially unnecessary animal testing under REACH. This is in breach of the REACH text demand that animal testing shall be used only as last resort. Thus there is an urgent need to enable sound and more efficient application of the other tools of risk assessment and management, to minimise use of animal testing.

This document reviews the current approaches to REACH Annexes VI-XI Exposure Based Adaptation (EBA) guidance, identifies pitfalls in the legal text and guidance, provides recommendations to registrants on the use and construction of EBA rationales and identifies areas where the REACH legal text must be improved to facilitate the use of EBA. These measures will aid the improves incorporation of EBA into testing strategies and therefore reduced animal use while still protecting human health. It further provides relevant endpoints for risk assessment while honouring the needs of hazard-based classification approaches. Although this document focuses on the use of EBA under EU REACH, the recommendations made would be relevant to other jurisdictions where exposure is a driver for determining the scope of the hazard and risk characterisation.

Implementation of Exposure driven testing within the EU REACH legal text

The stated purpose of the EU REACH regulation is to ensure a high level of protection of human health and the environment. Central to REACH is a requirement to identify and characterise hazard. The methods to achieve this vary based on a substance's manufacture or import tonnage. These requirements are considered cumulative, meaning the required information at each tonnage level must be fulfilled for the registered tonnage level and those below it. The REACH regulation has denoted four tonnage bands, each governed by its own annex:

- Annex VII: 1-10 tonnes/year,
- Annex VIII: 10-100 tonnes/year,
- Annex IX: 100-1000 tonnes/year, and
- Annex X: > 1000 tonnes/year

The tonnage bands are used as a surrogate for exposure potential to the public and the environment and the mandated data requirements are designed to provide sufficient information to evaluate potential risk based on the anticipated level of exposure. The annexes define the required standard information in Column 1 and the circumstance in which the requirements may be modified (adapted) in Column 2.

Use of exposure information to determine or modify the REACH data requirements is implemented in three different ways; the registrants tonnage band, the type of registration (full or intermediate under strictly controlled conditions) and Specific or General adaptation rules.

Tonnage band (Annual Production Volume, APV)

As indicated previously the information requirements necessary to support a registration are linked to the tonnage band of the registration, and where there are several registrants, the highest tonnage band needed by any registrant. A full registration at the 1-10t per annum level thus requires substantially less information than one for >1000t per annum. The principle behind this approach is an assumption that as APV increases, so too would the potential for exposure to humans and the environment and thus the risk. Therefore, more should be known about the higher tonnage substances so that we can ensure the high level of protection as stipulated in the regulation. Other principles are proportionality and practicality.

The data requirements for a high-volume substance are substantial and resource intensive to meet, and if these were required for all registered substances, they would place a substantial burden on the registrants of low-volume substances relative to the value of the substances on the marketplace. Therefore, it could be considered as disproportionate to require a substantial data package for low volume substances, particularly when one also considers the potential for exposure where there is equivalent hazard.

Unfortunately, the challenge with using annual production volume as the determinant of data requirements is that it does not well align with exposure potential to humans. Low volume substances could be used in ways leading to a high exposure level to an individual. Conversely high-volume substances may be used in ways which lead to very minimal exposure. Indeed, while reported chemical tonnages correlate well with estimated environmental media concentrations (van Gils et al., 2020) and resulted indirect (far-field) general human population exposure, they play a limited role in determining the potential for direct human (worker and consumer) exposure[1] (Bonnell et al., 2018), which often is orders of magnitude higher than that via environmental media. It is the type and conditions of use that determine direct human exposure to a greater extent, e.g. the product amount used per event, dilution factors, etc.

In addition, there is a further disconnect between tonnage band and exposure potential where there are many registrants of a low volume substance. For example, a substance with one registrant at 100-1000t level would require far more data compared to a substance with 12 registrants at 1-10t, even though there would be similar amounts of both substances on the market. The use of tonnage band therefore forms a compromise between the desire to get sufficient data to inform hazard characterisation and the need to have a workable legislation where registrants each know their obligations without placing a disproportionate burden on registrants of low volume substances. An alternative to the current tonnage-based REACH information requirements system for human health data could have been a more use-type oriented framework. In such a framework the uses would be ranked according to human exposure potential and depending on the relevant “sentinel” use and a base set of hazard information available for a substance the decision on the need for additional effects data is made.

[1] For consumer product exposures, more than half of the known higher probability exposures fell in the reported range of less than 100 tpy. In fact, for all substances with consumer exposures evaluated by Health Canada during this time, over 40% had reported commercial tonnages less than 10 tpy, with the majority reported as less than ~1 tpy

Registration type - Chemical Intermediates

Chemical intermediates are treated as special cases in REACH regulations and the information requirements are based on exposure potential. For on-site isolated intermediates and for transported isolated intermediates, in accordance with Articles 17 and 18, if the registrant can confirm the intermediate is used under strictly controlled conditions (rigorously contained through its entire life cycle) there is a requirement to provide any available existing information on physicochemical, human health or environmental properties of the intermediate. However, there is no obligation to fulfil the data requirements listed in Annexes VII to X. For transported isolated intermediates registered at >1000t per year the registrant is required to meet the information requirements listed in Annex VII. In confirming the intermediate is handled under strictly controlled conditions, there is no requirement for an exposure assessment. It should therefore be noted that even when a substance is rigorously contained throughout its life cycle, if its APV is high enough, chemical manufacturers should still provide selected acute hazard information. However, there is no requirement to assess the potential for repeated exposures or the potential for reproductive/developmental toxicity because exposures to chemical intermediates are expected to be brief and rare.

For both on-site isolated and transported intermediates, if strictly controlled conditions are not implemented then the registrants must meet the full data requirements listed in annexes VII to X depending on their tonnage band.

Specific and General rules for adaptation

For all registration types where there is a need to provide hazard data there are two options for using exposure to adapt or omit the data requirements under REACH:

- Specific Rules (column 2)
- General Rules (Annex XI)

Whether using a general or specific rule to adapt a data requirement, a registrant must cite the rule being used and document a thorough and well-reasoned scientific rationale. The rationale must be included under the appropriate headings in the substance dossier for the adaptation to be accepted.

Specific rules

For all data requirements listed in column 1 of annexes VII to X, column 2 sets out specific rules or conditions by which the standard information requirements may be omitted, replaced by other information, provided at a different stage or adapted in another way. The provisions in column 2 are endpoint specific and may be contingent on the physical/chemical properties of the substance, the availability of data for other endpoints, the classification of a substance and/ or the potential for exposure. For certain endpoints column 2 allows the possibility to omit the required study by considering exposure potential.

General rules

Annex XI specifies general rules for adaptation of the standard requirements set out in annexes VII–X. Annex XI distinguishes between three different cases, firstly where testing does not appear scientifically necessary (section 1), secondly testing is technically not possible (section 2), or thirdly testing may be omitted based on the exposure scenarios developed in the chemical safety assessment (CSA) (section 3). The latter point describes the so-called substance tailored exposure driven testing, known as exposure-based adaptation (EBA). It is important to note that for a full registration, only some data requirements (those involving the use of animal studies) are eligible for adaptation using an exposure-based approach.

Scope of the report

By setting data requirements contingent on a registrant's tonnage band and with tonnage band serving as a proxy for exposure potential, REACH sets a clear expectation that the potential for exposure (human health and the environment) should determine the data necessary to support safe use. This expectation is reinforced further by the modified data requirements necessary for different types of intermediates (on site, isolated; on site, non-isolated; transported), provided that these intermediates are handled under strictly controlled conditions, and the allowances of the testing annexes to modify data requirements based on exposure considerations.

The use of exposure elements to determine data requirements rather than mandate all substances have the same dataset is in recognition that the goal to ensure a high level of protection should not negatively impact competitiveness of the industry or lead to an unjustified increase in the amount of new toxicological studies requiring animal use. In this regard there is another important requirement that registrants generate new studies using animals as a last resort. This further emphasises the importance of utilising an exposure-based approach to determining adequate data requirements under REACH since it offers a clear mechanism to support a safety assessment without the need to generate new animal test data.

It is therefore clear what potential opportunities exist when EBAs are utilised, however it is also clear that there are inconsistencies in the different requirements and potential barriers to acceptance which make it very difficult for registrants effectively utilise EBA. One of these barriers is addressing the uncertainty associated with any approach which results in omitting a required study. But when considering how to address uncertainty, it is important to recognise that the data requirements laid out in the regulation already provide a clear picture of what data are expected for lower versus higher exposure potential substances, in some circumstances permitting dossiers where there is no expectation to generate data on potential hazards. Any exposure-based approach should therefore keep in mind the legislator's intent when considering what data are necessary to demonstrate the safe use of registered substances with different exposure potential in order to ensure consistency throughout the legislation.

EBA can be use for both human health and environmental endpoints. For the environmental endpoints, the use of exposure is evidently already implemented with exposure and risk-based triggers for higher tier studies listed in Annexes IX and X. In contrast, most studies required for human health endpoints are

mandatory versus triggered. In addition, the human health data requirements involve the largest potential animal use. Therefore, this assessment focuses mainly on human health endpoints and within this on the animal intensive repeated dose and reproductive toxicity studies. Nonetheless it is recognised that several of the general principles likely apply to both human and environmental endpoints.

Exposure Based Adaptations

As introduced previously, the possibilities for Exposure Based Adaptations are captured either in column 2 of annexes VII to X, or in Annex XI. These adaptations can be grouped into 3 different types of approach:

- Low Toxicity and Low Exposure (column 2)
- Low Exposure (annex XI)
- Risk-Based (annex XI)

Each of these will be reviewed in turn identifying what the requirements are and providing an assessment of what appears necessary in order to utilise the approach. ***Note that the assessment of what appears to be necessary in order to utilise the EBA within the REACH text is not a recommendation by the task force of what to do in each case.***

Column 2 Adaptations: Low Toxicity and Low Exposure

For the repeated dose, reproductive and developmental endpoints there are specific EBAs, and although they rely on the same overall approach whereby there should be low toxicity coupled with low exposure, there are some differences depending on the endpoint.

Repeated dose toxicity

For registrations of 10 tonnes or more, data on repeated dose toxicity is required. According to annex VIII – representing 10 metric tonnes or more – sub-acute (28 day, e.g. OECD (Organisation for Economic Co-operation and Development) 407 or OECD 422) repeated dose toxicity testing is required. This data requirement may be waived as indicated in column 2 if relevant human exposure can be excluded in accordance with Annex XI, section 3, most likely section 3.2(b) and/or (c). However, no further recommendation is provided at this tonnage level. This term implies exposure considerations only, contrary to the risk-based approaches developed for the other tonnage band requirements, as detailed below.

For registrations greater than 100 metric tonnes per year, according to annex IX a sub-chronic repeated dose toxicity test for the most relevant route of human exposure is required. Column 2 of annex IX gives the possibility to waive or adapt the standard information requirements according to specific rules, one

of which incorporates more specific requirements to support the exposure element. In line with this, the sub-chronic toxicity study does not need to be conducted if the substance is:

1. unreactive, insoluble and not inhalable, and
2. there is no evidence of absorption, and
3. there is no evidence of toxicity in a 28-day 'limit test',
4. particularly if such a pattern is coupled with limited or no human exposure.

This adaptation places far greater reliance on demonstrating the lack of reactivity, toxicity and bioavailability than it does on exposure, since the word 'particularly' indicates the exposure element is an additional, desirable, but not mandatory element of the adaptation. It also demands that toxicokinetic data are available even though a toxicokinetic study is not an explicit data requirement.

At this tonnage level usually acute toxicity studies, *in vitro* genotoxicity studies and a 28-day repeated dose study are available, and at least these data can be used to form the basis of the assessment of low toxicity. It is recognised that registrants, of their own volition, can provide additional information to aid in this assessment.

Column 2 of annexes VIII, IX and X also provide triggers for performing longer term or more specialised repeated dose toxicity studies. One of these triggers is a concern of enhanced exposure potential. Therefore, exposure is used not only to potentially reduce data requirements but can also increase them.

Implementing the exposure-based adaptation

The column 2 adaptation for a 28-day study refers to annex XI and will be discussed in the 'Low Exposure' section.

To waive the 90-day repeated dose toxicity study, one must meet all three of the criteria relating to toxicity, and provide some argumentation addressing the potential for exposure.

1. The substance needs to be unreactive, insoluble and not inhalable

This criterion is a part of the overall assessment of whether the substance is likely to become systemically available, and if not, whether it may still have properties that could lead to local effects. In the REACH endpoint-specific guidance the preferred approach to demonstrate a substance is unreactive and insoluble is discussed in a qualitative way (Endpoint specific guidance R.7.a, ECHA, 2017a). According to

this guidance, low reactivity, chemical and biological inertness or very low solubility (water) are examples of physico-chemical properties of a substance that usually suggest that the bioavailability of the substance will be low. However, the guidance offers no concrete criteria for any of the above qualifications nor does it address solubility in other solvents or lipids.

A. Reactivity

The other elements of this adaptation address the potential toxicological activity, therefore although not specifically stated it is assumed that reactivity relates to 'Chemical reactivity'. To address chemical reactivity, the available physical chemical data can be used as well as an assessment of functional groups known to be reactive, particularly under physiological conditions. As far as possible, the substance would be expected to be 'inert' and hydrolytically stable.

B. Insoluble

It is not specified whether the solubility in question here is water solubility or lipid solubility and no agreed threshold to conclude 'insoluble' in terms of g/L is provided in the legal text or guidance for this adaptation. If the intent is to address the ability of a substance to become absorbed then both water and lipid (e.g. triglycerides) solubility are important and the only way to conclude a substance is insoluble is using the appropriate OECD test guideline (OECD 105 – water; OECD 116 fat solubility) and analytical methods for the test substance.

With respect to water solubility, a practical cut-off would be a water solubility of ≤ 1mg/L at pH 2, 7 and 12. This is the same cut-off defined for aquatic toxicity testing of a 'poorly water soluble' substance (Endpoint specific guidance R.7.b, ECHA, 2017b, 2017c). A similar level seems appropriate for assessing lipid solubility.

C. Not inhalable

The REACH endpoint-specific guidance (ECHA, 2017a) indicates that acute inhalation tests need not to be performed for substances with a vapor pressure $<1 \times 10^{-5}$ kPa for indoor uses, and $<1 \times 10^{-4}$ kPa for outdoor uses. These values are equivalent to a saturated vapour pressure of 0.1 ppm for indoor and 1 ppm for outdoor. In principle, these cut-offs could also be applicable here to consider a substance as not inhalable. For particles, the ECHA (European Chemicals Agency) guidance considers particles larger than 100 µm as not inhalable.

However, it should be taken into account that particles between 10-100 µm median mass aerodynamic diameter (MMAD) will be trapped by the upper airways and swallowed, and lead to oral exposure rather than entering the small airways to become available to the lung. For waiving of inhalation studies of particulate materials (which are conducted with respirable particle sizes around 1 µm), the correct criterion is the respirable fraction below 10 µm, not the inhalable fraction, as the latter may not be capable of entering the lower airways.

2. There is no evidence of absorption

It is not specified with this criterion by what route there should be no absorption. Considering that the first criterion specifically requires the substance should be insoluble and non-inhalable, it is reasonable to focus here on the potential for absorption via the oral route, since an insoluble substance which is not inhalable is highly unlikely to be systemically available via the dermal and inhalation routes. Also, the preferred route of exposure for a 90-day study is the oral route for substances which are not gasses, vapors and for which aerosolisation is unlikely. It is also not specified what 'no evidence of absorption' is from a practical perspective. It would imply that the substance should essentially be non-detectable in the systemic circulation (e.g. blood) i.e. no systemic exposure. In order to achieve such an outcome, it seems inevitable that a full oral toxicokinetic study with both single and repeated exposures, use of radiolabel and appropriate analytical methodology would be the 'gold' standard study needed to generate the necessary information. Given the cost, potential complexity of such a study and animal usage; in addition to the fact that the substance is already shown to be unreactive and insoluble; requiring such an extensive study seems to be substantially disproportionate relative to the data requirement being adapted. Even if one could potentially satisfy this criterion, performing a 90-day oral study may be less resource intensive and provide certainty about having adequately address the data requirement.

There are two main data sources to assess absorption; in silico models or measured in vitro/in vivo data. Commercially available in silico tools such provide an estimate of systemic bioavailability based on structure and physical chemical parameters such as log Kow. However, considering that the substance should be insoluble in water and lipid, it is highly likely that models will struggle to predict systemic exposure since they are typically not capable of addressing active transport mechanisms.

In vitro assays using stomach or ilium and simulated gastric fluid are available (Youhanna and Lauschke, 2020), and these would be capable of determining passive diffusion and to a lesser degree active transport

through the gut. A reliable analytical method for the molecule and derivatives is still required, and the poor solubility of the test material would likely make the performance of the study technically challenging.

With respect to *in vivo* studies, since there is a requirement to perform a 28-day toxicity study to support this adaptation it is a possibility to add some form of toxicokinetic assessment into the study design, for example a blood time-course analysis following dosing (Saghir et al., 2012). Including this would potentially increase the number of animals and would require analytical methods for the parent and use of radiolabelled material (to ensure that absence of parent compound from the blood is not due to metabolism or hydrolysis). If a 28-day study is already available then if no alternative exists, a limited TK (Toxicokinetics) study would be necessary.

3. There is no evidence of toxicity in a 28-day 'limit test'

With the preference for using an oral dose route and the fact that the substance should also be non-inhalable, meeting this requirement would require an oral 28-day study using the limit dose (1000 mg/kgbw). No evidence of toxicity would typically require that there are no test article related 'adverse' effects observed.

4. 'limited or no human exposure'

In principle meeting the criteria 2 and 3 or 1-3 mentioned above should be enough to waive repeated dose studies at Annex IX and X level, in view of the way the next condition has been formulated in the legal text: "particularly if such a pattern is coupled with limited or no human exposure". As such it is not clear if there is a need to specifically address exposure here, however it is likely that a successful adaptation should have some assessment of exposure to minimise potential uncertainty associated with the approach.

In the ECHA guidance Chapter R5 on using an exposure-based adaptation (ECHA, 2011) some examples are provided for how to evaluate the potential for exposure (see Table 1), but it should be noted that there is no definition of 'limited' exposure, and it is technically impossible to provide experimental proof of 'no exposure', as this would require a detection limit of equal to or less than 1 molecule.

Table 1: Examples to illustrate a possible qualitative justification for waiving, to be justified in a weight of evidence approach in the registration dossier (taken from ECHA guidance document Chapter R.5)

Type of study to be waived (a)	**Substance properties or operational conditions.**	**Argumentation**
Repeated dose (90 days)	The substance is only used in closed systems, and occasional exposure is limited to maintenance or sampling tasks. A very small, well-defined and trained group of people is using strict risk management measures, and is exposed occasionally to low levels.	The use pattern of substance is such that long-term exposure can be excluded. Expert judgement is necessary to justify the case, for instance based on evaluation of the available acute toxicity and sub-acute toxicity indicating low toxicity. Depending on tonnage, additional information based on Annex XI requirements may be more appropriate (based on an ES).

This example requires as a minimum some written documentation of processes in place to minimise exposure and would require the exposure scenarios to be well defined.

Another way to look at how to address the requirement for “limited or no human exposure” is as an exposure which would lead to a Risk Characterisation Ratio (RCR) below 1 in the absence of the study to be waived. However, taking such an approach would require a risk assessment approach for a substance where all available data not only indicate an absence of any hazard, but also show it is not systemically available. As such, any toxicity benchmark would be somewhat arbitrary since it would be defined based on the use of a limit dose from toxicity studies (1000 mg/kgbw) and some form of assessment factors to determine a DNEL (Derived No Effect Level).

Given that there is already an exposure-based adaptation which utilises a risk assessment in Annex XI it seems appropriate that for using the column 2 adaptation for the 90-day study, it should be sufficient, and consistent with the guidance R.5, to document the use conditions and provide a qualitative assessment of exposure potential, indicating where controls are in place to minimise or prevent exposure.

Reproductive toxicity

At >10 tonnes, a reproductive/developmental screening study (OECD 421) is required (or a combined repeated dose and reproductive/developmental screen (OECD 422)). Like the requirement for a 28-day repeated dose study at this tonnage band, there is no specific requirement for exposure-based adaptation for this study in column 2 of annex VIII, but the general exposure-based adaptation in annex XI, section 3 may be used.

For registrations at 100 – 1000t, there is a requirement for a developmental toxicity study in one species. There is also a trigger for more extensive testing for reproductive (extended one generation study, OECD 443) and potentially a second species developmental toxicity study where there is some evidence of developmental toxicity but which is insufficient to allow a conclusion on classification. Assuming further testing for reproductive and developmental toxicity testing was not already triggered at 100-1000t, registrations at >1000t require both developmental toxicity studies and an assessment of reproductive toxicity in an extended one generation study.

Column 2 of annexes IX and X allows these requirements to be waived if:

1. the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available),
2. it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air)
3. and there is no or no significant human exposure.

In contrast to the column 2 adaptation for the 90-day toxicity study, exposure plays a more critical role for waiving the reproductive and developmental toxicity studies. For these studies it should be demonstrated that there is no or no significant exposure, whereas for the repeated dose, the exposure element was desired (‘in Particular…’) rather than mandatory. This indicates that the expectations for adapting reproductive and developmental toxicity endpoints are currently greater than for adapting repeated dose endpoints.

At these tonnage levels usually acute toxicity studies, *in vitro* genotoxicity studies, a 28-day and/or 90-day repeated dose study and a reproductive screening study are available. A toxicokinetic study is not part of

the data requirements at any tonnage level, so in order to meet the waiving criteria relevant toxicokinetic data need to be available or acquired.

Implementing the exposure-based adaptation

The criteria for adapting the reproductive and developmental data requirements are the same for both Annex IX and X and so they will be dealt with together.

1. the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available)

This criterion is somewhat like the requirement for adapting the 90-day repeated dose study, but rather than specifying a specific study (28-day) it is broader, encompassing all data available. This makes it a far more challenging criterion to address since there is no limitation in the term 'tests available' and as such any test capable of assessing toxicity should be considered in scope, potentially including ecotoxicity studies and studies not listed in the EU REACH annexes, irrespective of their relevance to the reproductive and developmental endpoint. Unfortunately, the REACH endpoint specific guidance in chapter R.7a and Chapter R.5 (guidance on adapting testing requirements) (ECHA 2017a and 2011) provides no information on this adaptation and what specific data should be taken into account.

Considering that a human health endpoint is in scope, it seems appropriate to limit the scope of 'available' studies to only those which inform on mammalian toxicity since the pattern of exposure and mechanisms of aquatic toxicity are not reliable indicators of human health endpoints. However, it is recognised that there are several assays using fish and invertebrates specifically designed to assess the potential for developmental effects (e.g. zebrafish embryo, nematodes) and if such assays are available then these should be considered as in scope for the assessment of developmental toxicity. With that said, regarding in *vitro* assays, caution should be taken when interpreting whether there is evidence of toxicity or not. Depending on the substance, very high concentrations of test material can be used which results in the test system being exposed to far higher concentrations than would be possible taking into account systemic exposure (estimated using *in vitro* to *in vivo* extrapolation). This is particularly important when considering that a requirement for this adaptation is lack of bioavailability. As such, when making the assessment of whether toxicity has been observed in *in vitro* (or *ex vivo*) studies, it should be acceptable that any toxicity test which does not consider the potential for systemic availability be excluded from the assessment.

Table 2 lists the human health studies that may be present at the tonnage levels corresponding to Annexes IX and X and the 'default' criteria by which it could be concluded a substance is not hazardous.

Table 2: Studies that may be available at Annex IX or Annex X tonnage levels

Study	**Outcome for "no hazard" conclusion**
Acute oral toxicity	LD_{50} (Lethal Dose with 50% mortality) ≥ 2000 mg/kgbw
Acute dermal toxicity	LD_{50} ≥ 2000 mg/kgbw
Acute inhalation toxicity	LC_{50} (Lethal Concentration with 50% mortality) ≥ 20,000 ppmV[a] or 20 mg/L[b] or 5 mg/L[c]
Skin irritation/corrosion	negative
Eye irritation/corrosion	negative
Skin sensitisation	negative
Ames test	Negative
In vitro cytogenicity study in mammalian cells or in vitro micronucleus study	Negative
In vitro gene mutation study in mammalian cells	Negative
Short-term repeated dose toxicity study (28 days), oral	NOAEL (No Observed Adverse Effect Level) ≥ 1000 mg/kgbw/d
Screening for reproductive/ developmental toxicity, oral	NOAEL ≥ 1000 mg/kgbw/d
Sub-chronic toxicity study (90-day), oral	NOAEL ≥ 1000 mg/kgbw/d

[a] for gases

[b] for vapours

[c] for dusts and mists

Considering the study outcome leading to a 'no hazard' conclusion in Table 2 it is still important to recognise that the criterion for this adaptation does not state 'non-hazardous' but rather states 'no evidence of toxicity'. As such, in addition to studies having the above outcome, they should also show that at all dose levels tested there was no observation of adverse effects, locally and systemically and, in particular, no evidence of systemic effects. It is recognised that such an interpretation can be very challenging for the variety of *in vitro* and *in vivo* assays, particularly those assessing local effects where a negative assay may still show some evidence that the test material is 'active' in the assay. However, given the focus of this adaptation is on no systemic absorption, as long as the results of assays do not indicate that the material has or could become systemically available then simply demonstrating a negative outcome from the study should be sufficient.

2. it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air)

This criterion sets two very significant challenges. Firstly, with the wording of this criterion stating a need for toxicokinetic data and the example that this data should be able to demonstrate no absorption based on blood concentrations plus assessment of excreta, it appears the expectation is that this criterion should be addressed by a comprehensive toxicokinetic assay. Secondly, it is unclear what is considered a relevant route of exposure. Considering this adaptation involves an assessment of human exposure (criterion 3), it is assumed that 'relevant route of exposure' relates to potential human exposure routes. As such, to address this endpoint a registrant should first determine relevant routes of exposure and subsequently generate data which allow a conclusion that there is no systemic bioavailability.

Addressing the route of exposure first, to identify the relevant route(s) of human exposure the registrant needs to assess how the substance is handled and used throughout its entire life cycle and determine what route(s) of exposure is likely. This presents a conceptual challenge, since it is also stipulated that there is no or no significant human exposure as part of this adaptation. As such the registrant would have to assess what route(s) could be 'technically' possible and this likely will be determined not only by how the substance is used, but its physical/chemical properties. It should be noted that if the substance is volatile [2] or forms an aerosol during use, it will be very difficult to utilise this adaptation given the potential for inhalation exposure and the need to demonstrate no or no significant exposure. In this situation it seems more appropriate to attempt the 'Low Exposure' adaptation detailed in Annex XI, section 3. For nonvolatile/non-aerosolised substances, one could utilise an assessment similar to that described for criterion 1 when adapting the repeated dose toxicity study to determine which routes of exposure could be technically feasible. In combination with the description of handling and use throughout the life cycle, this should allow an assessment of potential routes of exposure.

For nonvolatile and non-aerosolised substances, the dermal route of exposure is likely to be potentially relevant and as such, a dermal penetration study should be enough to demonstrate no potential for systemic absorption. It seems unlikely that the oral route of exposure would be ever relevant, even taking into consideration indirect exposure via the environment, since there is the requirement to demonstrate no or no significant human exposure. This criterion essentially eliminates the possibility for a release into

[2] The REACH endpoint-specific guidance indicates that acute inhalation tests need not to be performed for substances with a vapour pressure <1 x 10^{-5} kPa for indoor uses, and <1 x 10^{-4} kPa for outdoor uses and particles larger than 100 µm (ECHA, 2017a). In principle, these cut-offs should also be applicable here, meaning that if they are met the respiratory route is not relevant for risk assessment.

the environment that could lead to the substance becoming present in a drinking water source leading to toxicologically relevant human exposures.

3. No or No significant human exposure

This exposure requirement is essentially the same as that required for adapting the 90-day repeated dose toxicity study. Therefore, the same approach to documenting a qualitative assessment of exposure in accordance with guidance document R.5 is appropriate here.

Low Exposure: Adaptation according to Annex XI 3.2 b+c

Annex XI provides the only possible adaptation which depends solely on exposure information. To make use of this adaptation there is no requirement that a substance be non-reactive/non-hazardous/non-toxic and there is no expectation that the substance is not capable of becoming systemically available.

According to the general rules described in Annex XI, exposure-based waiving of repeated dose and reproductive toxicity studies required under Annexes VIII, IX and X is possible when any the following two sets of low exposure conditions are met based on a thorough and rigorous exposure assessment in accordance with section 5 of Annex I:

1) paragraph 3.2(b): where the substance is not incorporated in an article the manufacturer or importer demonstrates and documents for all relevant scenarios that throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f) apply;
2) paragraph 3.2(c): where the substance is incorporated in an article in which it is permanently embedded in a matrix or otherwise rigorously contained by technical means, it is demonstrated and documented that all of the following conditions are fulfilled:
    i) the substance is not released during its life cycle;
    ii) the likelihood that workers or the general public or the environment are exposed to the substance under normal or reasonably foreseeable conditions of use is negligible; and
    iii) the substance is handled according to the conditions set out in Article 18(4)(a) to (f) during all manufacturing and production stages including the waste management of the substance during these stages.

Implementing the exposure-based adaptation

Essentially, these types of EBA may be developed in a qualitative way as no quantification of risk is expected. However, it is true that qualitative approach may at some point acquire features of quantitative assessment, depending on the level of detail/effort required to demonstrate low exposure or no release. Once a quantitative assessment of exposure has been performed, some assessment of risk based on a toxicity benchmark is likely needed since for some substances even a low exposure may be a potential risk depending on the toxicity. However, this is addressed further in the risk-based adaptation section. Table 3 below provides the key exposure considerations to be addressed when developing qualitative EBA.

Table 3: Exposure considerations when developing a qualitative EBA

Strictly Controled Conditions	**No release from articles**
Manufacture and industrial intermediate uses only (no professional or consumer uses). Check for PROCs (Process Categories) and ERCs (Environmental Release Categories) descriptors that are not compatible with SCCs (Scientific Committee on Consumer Safety) (see ECHA's REACH guidance on intermediates, 2010)	Low concentration in products (e.g. concentration <0.1%)
Exposure is avoided primarily by technical means (e.g. closed system with limited breaches, rigorous containment by engineered controls, control of emissions to the environment) and organisational measures where appropriate[3].	Evidence of no significant unbound residual amount in a matrix and that covalent binding remains stable (i.e. encapsulation effect using e.g., transmission electron microscopy (**TEM**) techniques)
Automated continuous (not batch) processes, restricted entry	
Short term (acute) exposures and/or low use frequency	

[3] Detailed examples of technical measures can be found in Annex 7B of the previous regulation Commission Directive 2001/59/EC (28th ATP) (European Commission, 2001). Illustrative practical examples of technical means are also provided in a guidance document prepared by the French Chemical Industries Association (UIC / SICOS, 2017).

Strictly Controled Conditions	**No release from articles**
Documented proof of no exposure, e.g. workplace exposure modelling or monitoring and/or bio-monitoring (if available) ≤ LOD (Limit of Detection) for the majority of samples (Practical Guide 16, ECHA, 2014). Or can it be < 0.1 OEL (if OEL exists)? Note: the LOD must be sufficiently low, e.g. in the range of TTC (Threshold of Toxicological Concern) levels in the absence of reliable DNEL (see the Risk based approach document)	Documented proof of no exposure/release, e.g. using migration modelling, results from standardised leaching/bioelution tests (if available) ≤ LOD. Note: the LOD must be sufficiently low, e.g. in the range of TTC levels in the absence of reliable DNEL (see the Risk-based approach document)

More specifically, paragraph 3.2(b) of REACH Annex XI can be met using a qualitative assessment described in ECHA's guidance document R.5 (ECHA, 2011) and R.13 (ECHA, 2012a) and the Practical Guide 16 on Strictly Controlled Conditions (ECHA, 2014) to demonstrate low exposure conditions exist. There is no expectation that a quantitative exposure assessment be provided although it could form part of the documentation to demonstrate the control measures in place do lead to 'low or no exposure'. It should be noted that "no exposure "evidence under SCC (Strictly Controlled Conditions) is required not only for workers but the environment too. Thus, for EBA of human endpoints, the exposure route of 'man via the environment' needs to be taken into account as well.

For substances incorporated into articles there is an additional expectation as in paragraph 3.2(c) that information on the potential release from articles is provided. There are currently no formally agreed methods to measure leachables from a matrix or how to use the results from such studies in the context of EBA. However, protocols adapted from existing methods to assess release from articles using sweat simulant (e.g., CEN EN 1811:2011+A1:2015) artificial saliva or gastric fluid simulant (NEN-EN 71-3:2019) could be envisioned for assessment of substances other than metals (CEN, 2015; EFSA, 2017; CEN, 2019; ECHA, 2020). It should be noted that when assessing potential leaching from articles the study design should address reasonably foreseen conditions versus more extreme conditions designed to maximise the potential for leaching. The outcome of these studies should essentially show no leaching in order to conclude on 'negligible' exposure.

Notably, the expectation to provide monitoring/measured data as a documented proof of no (residual) release and resulted exposure that may occur despite of SCC (i.e. rigorous containment measures by

technical means) is debatable. In practice, an industrial exposure dataset is collected for a specific scenario of interest (e.g. tasks with potentially high exposure) and cannot be considered representative of typical/mean or low occupational exposure, the likelihood and magnitude of which are pre-determined and de-prioritised by initial expert judgement based on the implemented controls.

The same is true for the "no release from articles" scenario: measured data obtained for e.g. a monomer in polymer may not be representative of the release potential outcome for the finished plastic article. Often, registrants simply do not have access to the products safety testing data generated downstream. Therefore, conclusions derived using validated exposure in silico tools should be deemed acceptable.

Risk Based approach: Adaptation according to Annex XI 3.2a

The risk-based approach to adapting data requirements in Annexes VIII – X does not set any requirement for toxicity, bioavailability or reactivity of the substance in question. However, it does set out 3 cumulative criteria which set a very high bar for successfully justifying the use of this approach.

According to the general rules described in Annex XI (3.2a), exposure-based waiving of repeated dose and reproductive toxicity studies required under Annexes VIII, and all studies listed in annexes IX and X is possible when the manufacturer or importer demonstrates and documents that **all** of the following conditions of low risk are fulfilled:

a) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate no or no significant exposure in all scenarios of the manufacture and all identified uses;
b) a DNEL can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes. However:
    i) a DNEL derived from a screening test for reproductive/developmental toxicity is not considered appropriate to omit a prenatal developmental toxicity study or a two-generation/extended one generation reproductive toxicity study.
    ii) a DNEL derived from a 28-day repeated dose toxicity study is not considered appropriate to omit a 90-day repeated dose toxicity study.

c) the comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL;

Implementing the exposure-based adaptation

Although this adaptation gives the only opportunity to use a risk assessment to adapt data requirements in annexes VIII – X, it is implemented in a way that makes it very difficult to use successfully. The three criteria are cumulative, and each holds unique challenges.

a) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate no or no significant exposure in all scenarios of the manufacture and all identified uses;

Unlike the other adaptations where one can demonstrate no or no significant exposure using a qualitative assessment, for this adaptation there is a need for a quantitative exposure assessment. As with the previous adaptations there is still the lack of clarity regarding what is meant by 'no significant' exposure.

To date, there are no agreed acceptance criteria or rule-base for determining "no significant" exposure other than following a quantitative approach highlighting the relative nature of (chemical) exposure, i.e. significance of exposure can only be evaluated in comparison to a health-based benchmark value (e.g. DNEL).

b) a DNEL can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes.

The wording of this criterion, including the footnote to this text in Annex XI section 3 introduces a major challenge when attempting to use the risk-based approach.

First, the requirement for a DNEL relevant to both the data requirement to be omitted and for risk assessment purposes places a clear restriction on what data can be used to derive the DNEL. For example, in the event a 28-day study or a reproductive screening study is being adapted, in theory one would need to have a study addressing both repeated exposures and reproductive parameters in order to derive a DNEL.

Alternatively, one could theoretically use acute toxicity studies with conservative assessment factors to derive a DNEL, but in our opinion, acute, single exposure toxicity studies would not adequately address a repeated exposure scenario nor provide information on potential for reproductive findings. Consequently, although it is possible within the REACH legal text to use an exposure adaptation for the 28-day and reproductive screening studies, it is evident that using a conventional DNEL approach would not be possible for a risk-based adaptation.

An alternative approach which could be appropriate here is a Threshold of Toxicological concern approach.

The threshold of toxicological concern (TTC) approach is a screening tool that has been developed in order to assess substances of unknown toxicity present at low levels in the diet (Kroes et al., 2004). Application of the TTC approach requires only knowledge of the chemical structure of the substance concerned and information on human exposure, for which there is confidence that it is not an underestimate. It utilises generic human exposure threshold values (also called TTC values) that have been established for substances grouped according to their chemical structure and likelihood of toxicity. Since the concept cannot be applied to all chemical structures, e.g. inorganics and dioxins are excluded and should be covered by a chemical specific assessment (see e.g. Kroes et al., 2004; EFSA, 2012; EFSA and WHO, 2016), it is imperative to know the structural identity of the chemicals to be evaluated. This introduces a challenge for ill-defined substances such as UVCBs. The latest guidance on the use of TTC is given by the European Food Safety Authority (EFSA, More et al., 2019). TTC levels are specified in the tables 4 and 5 below.

Table 4 Oral TTC values for consumers (EFSA, More et al., 2019)

Chemical class	**µg/person/d**	**µg/kg bw/d**
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1800	30

Table 5 Respiratory TTC values normalised for consumers (Escher et al., 2010)

Chemical class	**TTC values***		
	ppm	**mg/m³**	**µg/person/d**
Cramer Class I	3.6×10^{-3}	8.9×10^{-3}	180
Cramer Class III	2.4×10^{-5}	1.8×10^{-4}	4

* Excluding genotoxic chemicals

The values given by Escher et al.,2010 were normalised for consumers (i.e. 24 hours/day, 7 days/week) and thus need to be adjusted for the workplace conditions.

There are no dermal TTC values based on a database of dermal toxicity studies. Therefore, it is proposed to apply the oral values, assuming equal dermal and oral absorption, which can be considered a worst case.

It should be noted that the TTC levels specified here are quite low and can only be used for exposure-based waiving, provided the exposure assessment methods available are sensitive enough to prove that the very low levels of exposure associated with the various TTC levels are not exceeded. For many chemicals, however, a TTC approach will not be feasible as this level of exposure (only available for the oral route) is too low to be practically measured with the current state-of-the art exposure measurement or modelling approaches.

When adapting the annex IX and X requirements for repeated dose toxicity and reproductive/developmental toxicity the current wording of Annex XI section 3 is still highly restrictive due to the specific limitation that the shorter term repeated dose toxicity study (28-days) and reproductive screening study cannot form the basis of the DNEL derivation for repeated dose and reproductive/developmental endpoints respectively. This forms a clear contradiction to the default risk assessment of chemicals in the volume band <100 mt/y, which uses the 28d and reproductive screening studies for DNEL derivation. The requirement that the study forming the basis of the DNEL is also relevant to the data requirement being adapted also suggests that one could not use the DNEL from a 28-day study to adapt a reproductive or developmental study since the 28-day study provides limited information on reproductive toxicity and no information on developmental toxicity. This additional requirement also suggests that a DNEL derived from a 90-day study would not be suitable to adapt a developmental toxicity study since it provides no data on developmental toxicity. In fact, other than an existing developmental

study it is difficult to determine what study would be appropriate to form the basis for a DNEL to adapt a data requirement for this endpoint. Consequently, even in the scenario where a 28-day study and a reproductive screening study are available, according to the current text of Annex XI 3.2 a, these cannot be used as part of a risk-based exposure adaptation.

As with the 28-day and reproductive screening studies, a TTC approach could also be used for the annex IX and X data requirements, however it seems inappropriate to use such an approach when data may exist from substance specific lower tier studies.

Assuming a suitable study can be identified, the criterion also stipulates that the DNEL should be derived taking full account of the increased uncertainty resulting from the omission of the information requirement. This suggests that either an additional assessment factor should be used when deriving the DNEL or that more conservative assessment factors should be used. If the substance is not hazardous in the available studies, the need to derive a DNEL also raises the question of how to derive a DNEL for a non-hazardous substance.

For other endpoints addressed in Annex IX and X, for example *in vivo* genotoxicity, it is unclear if a risk-based exposure adaptation is possible. The current regulatory paradigm for genotoxicity is to assume no threshold, consequently it is uncertain if setting a DNEL/DMEL (Derived Minimal Effect Level) is possible, and from which study. Recent research into using a risk-based approach for genotoxic substances does illustrate how *in vivo* genotoxicity data could be used to derive a point of departure for a risk assessment (Luijten et al., 2020) and so it could be foreseen that a risk-based approach is in principle feasible for genotoxic substances, however this will not be discussed further in this report.

c) the comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL;

This criterion introduces the need for the risk assessment but sets the expectation that exposures be well below the DNEL without adequately defining what this means. The current guidance for using an exposure-based adaptation does not illustrate what is ‘well below’ the DNEL although it is evident that a RCR < 1 allowed in a standard REACH chemical safety assessment would not be acceptable. Additional conservatism currently sought for EBA-type RCRs may stem from the undefined uncertainty in estimated/predicted exposure (i.e. how conservative it is in terms of the likelihood of underpredicting exposure for a given scenario) and/or the newly derived DNEL (due to omission of the study).

One would assume that considering the first criterion to require no or no significant exposure, attaining a low RCR for all exposure scenarios would be likely, however it is highly dependent on the DNEL and capability of the exposure assessment tools used.

As discussed above, the uncertainty may be largely compensated for in DNEL derivation. Introduction of an additional uncertainty factor on exposure or RCR side will then be considered redundant, as there should be no difference in expectations of (sufficient) level of confidence in exposure estimates generated for REACH CSA and EBA purposes. In fact, it is irrational to permit RCRs<1 in the first instance and demand RCRs<<1 in the other, given that same exposure assessment tools tend to be used for both. Moreover, the development of a uniform exposure uncertainty factor to be applied across different exposure and contributing scenarios in EBA to address concerns of insufficient conservativeness of certain exposure models is not possible. Although not definitive, numerous research studies indicate that the distance between predicted and measured exposure varies significantly depending on the PROC/PCs (Product Category) (Hesse et al., 2015; Franken et al., 2020; Schlueter et al., 2020).

Overall, as currently implemented the use of the risk-based exposure adaptation is extremely challenging to use and unlikely to be feasible for adapting all annex IX and X requirements for the same substance.

Assessment of Exposure-Based adaptation approaches

When comparing the general rules for exposure-based adaptations with the endpoint specific exposure-based adaptations and tonnage specific data requirements for intermediates and full submissions, several points warrant further discussion.

Inconsistent use of 'Exposure' as a driver for data requirements

The different data requirements linked to registration tonnage band show that for substances registered in a low tonnage band where there is an assumption of low exposure potential, less data is needed to demonstrate safe use relative to substances registered in a higher tonnage band. However, for substances where it is demonstrated that irrespective of tonnage band there is very low exposure (no or no significant exposure) there are either requirements to demonstrate no toxicity, reactivity, solubility, and bioavailability, and/or requirements to provide detailed documentation of how the substance is rigorously contained to prevent exposure. This makes the use of exposure-based adaptations challenging and thus

it is more likely that higher tonnage-band substances will end up being tested more extensively, irrespective of exposure potential and whether the generated data would meaningfully impact safe use. It follows that the current tonnage-based REACH information requirements system for human health data could be transformed into a more use-type oriented framework, to make it more relevant for the protection goals of REACH.

Inconsistent requirements for 'low toxicity' and bioavailability

Column 2 specific adaptations for repeated dose toxicity and reproductive/developmental toxicity both require that the substance be of 'low toxicity', however it is handled in different ways for the two endpoints (See section 'Column 2 Adaptations'). It is likely that were a registrant to invest the effort to demonstrate that a substance does not require testing for one of these endpoints, they would apply the same approach for the other. As such, it is unclear why there is a difference in the requirement to demonstrate low toxicity.

In addition to this, the criteria for each of these specific adaptations appear to introduce a lot of redundancy. If a substance is insoluble and not inhalable then the probability that it is systemically bioavailable is low. As such, why also require toxicokinetic data to show lack of bioavailability?

Concerning Annex XI and given that all specific and general adaptations require a demonstration of low exposure, it is not clear why in endpoint specific adaptations there is the additional requirement to demonstrate low toxicity and bioavailability.

Value of data from 28-day and reproductive screening studies

With respect to repeated dose toxicity, there is some inconsistency in how the data from a 28-day repeated dose toxicity study can be applied when adapting the 90-day study requirements. According to column 2 of Annex IX, section 8.6.2 it is stated that a 90-day study is not required when a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure. As such the data derived from a 28-day study is sufficient to support waiving the 90-day study requirement, irrespective of exposure. Similarly, in Column 2 of annex IX, section 8.6.2, the data from a 28-day study are required to form part of the argument to adapt the data requirement for a 90-day toxicity

study, whereby there are no adverse effects observed in the 28-day study. However, when attempting to use the general considerations for exposure-based waiving it is stated specifically in annex XI, footnote to paragraph 3.2 (ii) that a DNEL derived from a 28-day study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.

There is a similar inconsistency with respect to the reproductive/developmental endpoints, where the DNEL derived from a screening study (e.g. OECD 421 / 422) cannot be used to waive higher tier reproductive and developmental toxicity studies according to annex XI, footnote to paragraph 3.2 (ii). However, in column 2, Annex IX, section 8.7, there is a requirement for 'no evidence of toxicity seen in any of the tests available' as part of the adaptation to waive the higher tier studies. Although not specifically stated, the OECD 421 or 422 studies could form part of the 'tests available', and as such the data from this study (in conjunction with other data) would support waiving the higher tier studies.

When comparing the data requirements for different tonnage band registrations with the Annex XI, footnote to paragraph 3.2 (ii) requirements for exposure-based adaptations there is an inconsistency in how the REACH legal text uses different studies to form the basis of a DNEL and inform a risk assessment. Considering the goal of REACH to deliver a high level of protection of human health and the environment, the data requirements have been established for each tonnage band to provide the information necessary to support the safety assessment. For a substance registered at 10-100t there is a requirement for a 28-day repeated dose study and a reproductive screening study (or the combined OECD 422 study). If a 10-100t substance is classified as hazardous, the DNEL from these studies is used in the risk assessment to demonstrate safe use. This is irrespective of the types of uses, level of exposure or severity of the hazards observed in the studies. If the substance is not classified as hazardous there is no requirement to perform a risk assessment. However, within the context of using an exposure-based adaptation, as shown above, a DNEL derived from the lower tier studies cannot be used to adapt the higher tier studies. This is irrespective of whether the substance is hazardous. If a DNEL from a screening study is acceptable to support safety assessment irrespective of exposure and use, it should also be acceptable for supporting a safety assessment as part of an exposure-based adaptation.

There is therefore an inconsistency when considering when an exposure assessment alone is enough to support and exposure-based adaptation.

Taking this into consideration, it is clear that although there are several different ways that exposure has been employed when determining the scope of the hazard and safety assessment under REACH, there are

a lot of inconsistencies which make the use of exposure-based approaches to adapt testing requirements challenging to navigate, leading to inefficient use of limited resources and unnecessary animal testing.

Recommendations

To avoid redundancies/ambiguity and misinterpretations of the legal text in REACH Annexes VII-XI it is recommended to better distinguish between the concepts of toxicological activity (hazard), systemic absorption and no relevant/no significant systemic exposure. Importantly, it should be clarified that demonstration of no significant (external) exposure or no absorption (i.e. systemic exposure) should be enough to waive an effect study (e.g. in Annex IX 8.7), i.e. demonstration of both is redundant.

It is also recommended to revise the legal text of Annex XI section 3.2(a) (along with the footnote) to:

- Clearly articulate it implies a risk-based approach, i.e. combine conditions 3.2(a)(i) and 3.2(a)(iii);
- Allow to use low tier and screening studies for DNEL derivation (with additional data-based assessment factors, if appropriate);
- Rephrase the requirement for exposure to be below the derived DNEL (as opposed to “well below”);

Another recommendation is to recognise and adopt the widely applicable TTC approach for the development of REACH EBA. The TTC is basically a worst-case estimate of the toxicity of compounds expressed as an exposure threshold. If exposure information shows that TTCs will not be reached, this could be used as screening tool to set aside a chemical with “very low” exposure. If the measured or predicted exposure concentration comes close to the TTC this could trigger further information on the toxicity of the chemical. This is certainly a promising approach that can limit animal testing, when combined with adequate information on the use of and exposure to chemicals.

Finally, a more general recommendation is provided to transform REACH information requirements system for human health into a more exposure-driven (intelligent) hazard data generation framework, as already implemented for environmental endpoints. The ultimate goal is to enable assessment strategies that will eventually lead to an efficient way of risk assessment and risk management of chemicals. Divergent interpretation by various stakeholders of the purpose of REACH information requirements leads to conflicting views on the appropriate/suitable methods for data generation. It is unrealistic to expect that the use of (Q) SARs alone or in-vitro alone will be able to completely replace the animal tests required for risk assessment in general, or under REACH. It is the interplay with exposure, which will enable to waive a large amount of animal testing and focus on these substances and uses that pose the highest risk.

Ignoring the exposure element leads to generation of non-relevant data, which take time, use animals and incur costs to registrants and regulators.

A Tiered Approach to adapting data requirements under REACH

General Considerations

Any type of EBA of standard hazard information requirements should be developed in view of a base set of hazard information already available for the substance and the purpose of generation of new information (e.g. classification & labelling and/or risk assessment). EBA can serve as a measure of the need to acquire an additional understanding of the endpoints; testing is one way in which such an understanding can be obtained.

The EBA should be reconsidered if a new use is proposed/planned, unless there is a concept of hierarchy of uses in place and it can be demonstrated that the new use will not result in exposure higher than predicted in EBA. However, if the whole REACH human health data acquisition framework was more risk-driven and integrated information on type of use and exposure potential early on, EBA in its current form would not be needed.

Additional data acquisition does not reduce risk, rather it serves to reduce actual or perceived uncertainty leading to a more robust risk characterisation. In the context of EBA, clear guidance is therefore needed as to how/when risk characterisation is given precedence over hazard identification. That is, to answer the question of whether the omission of certain tests using exposure criteria might lead to an incomplete or incorrect risk characterisation.

The cornerstone of EBA discussion is a postulate that generation of additional effects information would not lead to an improvement of estimated risk level and the existing/prevailing risk management practice. The process of responsible risk management should be distinguished from the process of hazard information acquisition, acknowledging that hazard classification and communication only represents one aspect of risk management. Simplistic box-ticking approach/mindset without linking the testing strategies to exposure considerations hinders progress towards achieving the 3Rs goals. Hence, exposure assessment should take place early on in the risk characterisation process. Strategies for intelligent testing should integrate information on real-life exposure patterns and TTC type concepts as mediators for determining ‘added value’ of tests. In the end, if safe use (no risk) needs to be confirmed/enforced, why not start exposure assessment upfront to inform hazard assessment?

Generic approaches for targeted risk assessments have been developed and verified in the past (e.g. Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century Project (RISK21), Control of Substances Hazardous to Health (COSHH) Essentials, ECETOC TRA (Targeted Risk Assessment)). They provide evidence that extensive effects data are not required to effectively manage risks. While managing risks on the hazard side may seem generally easier, such an approach can potentially lead to undesirable negative consequences (e.g. regrettable substitutions, restriction of beneficial uses, and unnecessary use of test animals). It also ignores potentially relevant exposures of individuals to not classified substances.

In general, all types of chemicals can be subject to EBA. The burden of proof to demonstrate "low" exposure is a function of the length of the supply chain and complexity of the use pattern: the less diverse and the lower the number of uses, the greater the likelihood that EBA criteria will be met. EBA cannot be seen as a 'soft option' or an 'easy solution'. The supporting justifications may go beyond what would typically be expected in Exposure Scenarios developed for standard REACH chemical safety assessment.

Examples of Exposure Based Adaptations within other EU Chemical Legislations

When considering how to better make use of EBA under REACH, one can consider where a similar approach is employed in other legislation. An example where generation of effects information based on exposure considerations has been incorporated in the legislative guidance documents include the guidelines of the European Scientific Committee on Food (SCF) for substances used in (plastic) food contact materials (EFSA, 2016). The approach implements the concept of tiered exposure-based testing as defined by migration rates into food simulants (see Table 6 – Comparison of effects data requirements in REACH and FCM (Food Contact Material) regulations) and integrates the concept of the Threshold of Toxicological Concerns (TTC) in a risk assessment process to justify the waiving of specific toxicological tests (European Commission, 2004 and 2006).

Table 6: Comparison of health effects data requirements under the EC (European Commission) 1907/2006 (REACH) and EC 1935/2004 (FCM)

REACH *	FCM based on EFSA, 2016
1-10 t/y	**Tier 1: human exposure < 1.5 ug/kg/d or < 30 ug/kg/d and Cramer I ****
Ames (+ follow up if positive)	Genotox in vitro (in vivo follow up if positive)
Acute tox (oral)	Available info from literature
Skin and eye irritation	
Skin sensitisation	
10-100 t/y	**Tier 2: 1.5 ug/kg/d < human exposure < 80 ug/kg/d**
In vitro gene mutation	Extended/modified 90d oral repeat study in rodents
Chromosome aberration	
28d repeat study (rat)	
(existing) toxicokinetic data	
Acute tox (2nd route)	
Reprotox screening study	
100-1000 t/y	
Reprotox	
Developmental tox	
In vivo genotox (if in vitro positive)	
90d repeat study	
>1000 t/y	**Tier 3: human exposure > 80 ug/kg/d**
Carcinogenicity + chronic tox (concern based)	ADME (Absorption, Distribution, Metabolism, and Excretion) studies
	Carcinogenicity
	EOGRTS (Extended One-Generation Reproductive Toxicity Study in rodents or multi-gen study)
	PNDT in rats or rabbits
Developmental tox (2nd species)	1 year repeat study (in rodents)

* - Assuming the total EU population of 446 million, REACH tonnage bands translate into: 0.1, 1.0, 10.2, 102.4 ug/kg/d for 1, 10, 100 and 1000 t/y, respectively.

** - Exceptions are: (1) if there are existing data indicating the potential to affect endocrine or neural systems; (2) for substances with a high potential to accumulate in humans; (3) for nanomaterials, even if the non-nanoform material has been evaluated and approved for FCM.

For cosmetic ingredients, the notes for guidance (SCCS, 2018) indicate that where an ingredient is demonstrated not to be systemically available, higher tier toxicity studies (including repeated dose and reproductive/developmental data) are not required.

The Biocidal Products Regulation (European Commission, 2012) also provides the possibility to waive testing on the grounds of limited exposure, poor solubility and strong absorbance to organic matter. Mammalian toxicological data may be waived for certain specific product type factors if the toxicological

profile of the active substance allows for it. In all cases acceptable justification must be provided. The justifications are considered on a case-by-case basis.

Tiered Approach to Exposure Based Adaptations

With the above considerations in mind, the taskforce is proposing a tiered approach to adapting data requirements which could replace the existing adaptations in Annexes VII-XI.

Tier 1

A: Low toxicity and low systemic availability

OR

B: Low exposure

Tier 2

Risk-based approach

The two possibilities outlined in Tier 1 align to some degree with the existing Column 2 adaptations for Annex IX and X mammalian toxicity endpoints and the annex XI general adaptation (3.2(b) and 3.2(c)). The Tier 2 approach aligns with the existing adaptation detailed in annex XI, 3.2(a). The intent here is that a registrant may be able to use either of the Tier 1 approaches to adapt data requirements, but if these are not possible or suitable, then the Tier 2 Risk-based approach can be utilised.

Tier 1A – Low toxicity and low systemic exposure

It is evident that a high expectation has been set within the REACH legal text for registrants attempting to demonstrate no further testing is required due to a low order of toxicity and bioavailability. It is therefore concluded that the legislator anticipates very few substances to qualify for an adaptation based on toxicity and bioavailability. However, one must also take into consideration the broader goals of ensuring a high level of protection of human health and the environment while also using animal testing as a last resort. When considering this, performing the higher tier, animal intensive studies on substances which have minimal toxicological activity and low systemic exposure would not generate information which would meaningfully contribute to these goals of REACH. Such testing would therefore qualify as an unnecessary use of animals. While we must consider that using an adaptation based on low toxicity and low bioavailability should require a robust justification supported by sound data, the criteria should be designed to practically enable the goal of using animals only as a last resort.

The fundamental basis for this approach is the hypothesis that a substance which has low systemic exposure, low bioaccumulation potential AND low toxicity is very unlikely to demonstrate evidence of toxicological effects in more extensive studies which would then influence the hazard characterisation and risk assessment. It is also important to recognise that systemic availability is a measure of systemic 'exposure' potential. The REACH legal text already sets the precedent for allowing less toxicological data to be generated for lower tonnage/low exposure potential substances, therefore by employing this logic, a substance which has low systemic exposure can be considered as equivalent to a substance with low external exposure potential. Therefore, it is justified to adapt the data requirements to reduce the need for higher tier animal studies where it can be demonstrated that the systemic exposure potential is low.

Low systemic exposure

When utilising this approach, consider first the potential systemic exposure via 'Relevant routes' of human externalexposure for the substance, since the requirements of REACH are substance specific and the policy goal is to ensure a high level of protection of human health. For each substance the relevant routes of potential human exposure should be identified based on the physical/chemical properties and the identified uses. The second consideration is what constitutes 'Low' systemic availability.

Relevant routes of external exposure:

Oral route

For substances subject to, and solely regulated by REACH, direct exposure via the oral route is typically not a relevant route for humans. However, when one considers the potential for indirect exposure via the environment or oral exposure to aerosols, it is difficult to completely discount the oral route of exposure. Consequently, it is recommended that the oral route of exposure be considered as relevant when assessing systemic exposure.

Inhalation route

For non-volatile or non-respirable substances, the inhalation route may not be a relevant route of human exposure. The REACH endpoint-specific guidance indicates that acute inhalation tests need not to performed for substances with a vapour pressure <1 x 10^{-5} kPa for indoor uses, and <1 x 10^{-4} kPa for outdoor uses (ECHA, 2017a). For particles, the ECHA guidance considers particles larger than 100 µm as not inhalable. However, it should be taken into account that particles between 10-100 µm median mass aerodynamic diameter (MMAD) will be trapped by the upper airways and swallowed, and lead to oral exposure rather than entering the small airways to become available to the lung. For waiving of inhalation studies of particulate materials (which are conducted with respirable particle sizes around 1 µm), the correct criterion is the respirable fraction below 10 µm, not the inhalable fraction, as the latter is not capable of entering the lung. These criteria could therefore be used as a basis for determining whether inhalation would be a relevant route of human exposure.

For volatile substances, or substances where exposure to an inhalable/respirable aerosol or mist is possible, inhalation must be considered as a relevant route of human exposure when assessing low systemic availability.

Dermal route

The dermal route of exposure is likely to be a relevant route of exposure for humans for most substances.

What is 'Low' systemic exposure and how to demonstrate this?

When defining this approach, a conscious decision was taken to recommend 'low' systemic exposure versus 'no' systemic exposure. The driver for this is the significant challenge posed when attempting to demonstrate no systemic availability from an analytical perspective. The inherent challenge to using an

approach where 'low' systemic exposure is required, is defining a cut off or threshold which is scientifically defensible while also meeting policy objectives. To define such a cut off level it is also important to take into consideration that a substance must also have low toxicity to make use of this adaptation and that other factors such as bioaccumulation potential should be considered.

It is also important to use the most appropriate metric for assessing systemic exposure, and it is proposed to use the Area Under the Curve (AUC) as this gives the complete picture of systemic exposure versus a more simplistic parameter such as % of total dose in the blood.

One pathway through this is to set a level which takes into consideration extrapolation of animal data to humans when deriving a DNEL.

What would it mean for example, to use acceptable 'low' level of systemic exposure of 1% of the dose given in a toxicity study? For a 28-day repeated dose toxicity study with a limit dose NOAEL of 1000 mg/kg bw (as 'no toxicity' is required), the systemic dose would therefore be 10 mg/kgbw/d, i.e., the same systemic dose one would expect for a substance which is 100% bioavailable (default assumption ECHA) and dosed at 10 mg/kg bw. If this dose is a NOEL, then in principle, a DNEL for systemic effects could be derived for both substances starting from 10 mg/kg bw.

For the oral route and using an assessment factor of 1200 (10 interspecies, 10 intraspecies, 6 sub-acute to chronic, 2 quality of the database), this systemic dose of 10 mg/kg bw/d would lead to a systemic DNEL of 0.008 mg/kg bw/d, or 8 µg/kg bw/d. This can then be compared to the oral threshold for toxicological concern (TTC) value of 30 µg/kg bw/d for Cramer Classes I substances (those deemed to be minimally toxicologically active). The TTC value is an 'external' exposure value and so it must be adjusted to account for systemic availability since we are making the comparison with a systemic DNEL. To convert to a systemic TTC value a conservative value of 50% systemic availability via the oral route is taken. (Assumption of 50% oral bioavailability is the default approach within the EU REACH guidance Chapter R.8 (ECHA, 2012b) for route to route extrapolation from oral to inhalation routes). Therefore the 'systemic' oral TTC value for Cramer Class III substances is taken to be 15 µg/kg bw/d. This level is approximately 2 times greater than the systemic DNEL of 8 µg/kg bw/d for a substance with 1% systemic bioavailability and no adverse effects at 1000 mg/kg bw/d.

If the policy objectives of ensuring a high level of human protection is also considered, it seems appropriate to recommend a benchmark for low systemic availability be set at 1% which would lead to an

exposure of approximately 8 µg/kgbw/d which would still be lower than the TTC for Cramer Class I substances.

Although the TTC approach has not been formally validated against the dermal and inhalation routes of exposure, from a pragmatic perspective it is proposed to use a similar rational and a 1% cut off value for systemic exposure, irrespective of dose route.

In order to assess systemic availability, the most compelling evidence would come from an *in vivo* toxicokinetic study. However, it is recommended to take a tiered approach to the assessment in order to assess whether using this adaptation is feasible and avoid unnecessary animal testing. As part of a tiered approach one can first consider physical/chemical properties and physical state and utilise QSAR ((Quantitative) Structure Activity Relationship) tools to estimate bioavailability. If this information indicates that bioavailability will be low, then either *ex-vivo* or *in vitro* assays could be used without the need to progress to an *in vivo* assessment. For performing an *in vivo* assessment of systemic exposure, it is strongly recommended to incorporate this as an additional endpoint into other required studies such as the 28-day repeated dose toxicity study (Saghir et al., 2012). This approach has advantages from an animal usage perspective and allows for an assessment of bioavailability following a repeated dose regimen. For the assessment of dermal bioavailability an *in vitro* skin penetration study is generally accepted as a reliable method. Ultimately, it is important that irrespective of the assays utilised, a robust weight of evidence must be generated to demonstrate that systemic availability is below an accepted threshold.

Bioaccumulation potential

In addition to agreeing on the cut off value for systemic exposure it is necessary to address potential for bioaccumulation. If the substance is absorbed to a minimal degree, but has the potential to accumulate, the level of systemic exposure after a longer period of time may reach a level where there may be a toxicity concern which would not be adequately addressed via shorter term studies. Substances which have the potential to bioaccumulate may not be suitable for this adaptation. In those situations, it may be more appropriate to perform a 90-day repeated dose study to confirm that longer term dosing does not produce and adverse effects. If physico-chemical properties and structure of the substance indicate a potential concern for bioaccumulation, for example in vitro metabolism studies should be applied to investigate the concern, or repeated dose in vivo bioavailability can inform on bioaccumulation.

Low toxicological activity

In column 2, Annexes IX and X, low toxicological activity is defined (in parentheses) as "no evidence of toxicity seen in any of the tests available". For the purposes of this proposal, toxicity should be interpreted as 'adverse effects'[4], since adaptive effects are not in of themselves considered to be evidence of toxicity. It is important to make this distinction since toxicological studies are designed to identify the presence of adverse effects, with the interpretation of said studies as positive being linked to the specific toxicity parameters measured when 'adverse' changes are demonstrated.

If it is considered that an approach to use low systemic exposure and low toxicity to adapt animal studies listed in Annexes IX and X, then in principle the studies in Annexes VII and VIII should be available (unless other column 2 or Annex XI adaptations were utilised).

Taking the assumption that the Annex VII and VIII studies are available, below is a proposal for what can be considered as 'low toxicity':

- Acute toxicity (via relevant exposure routes): no lethality up to limit dose (or if dosing is limited by physical properties, no effects observed up to the maximum dose possible); No evidence of systemic effects
- Local effects: no effects leading to classification
    - For LLNA (Local Lymph Node Assay)/ GPMT (Guinea Pig Maximisation Test)/ In vitro skin sensitising potential assays – outcome should be negative i.e. Threshold for skin sensitisation is not reached
- Genotoxicity: Negative
- Repeated dose toxicity/Reproductive/developmental studies – NOAEL is 1000 mg/kgbw
    - Dose route – ideally that leading to the 'highest potential' for absorption (oral, or inhalation for 'volatile' subs).

[4] **Adverse Response** • A biochemical, morphological or physiological change (in response to a stimulus) that either singly or in combination **adversely affects** the performance of the whole organism or reduces the organism's ability to respond to an additional environmental challenge (Lewis et al., 2002).

Summary

This approach to adapting repeated dose and reproductive toxicity findings still sets a high bar for both toxicity information and bioavailability data. However, if a substance meets the proposed criteria then it is clear further testing would be unlikely to yield data which would modify the hazard characterisation and risk assessment. A further refinement of this approach could be to adapt the threshold for systemic availability based on the toxicity potential. If a substance is essentially inert, then it could be argued that a higher systemic availability could be acceptable and such an approach could also be supplemented by exposure and use information. However, these refinements would warrant further assessment to determine how best to balance systemic availability, toxicity and exposure.

Tier 1B – Low exposure approach

EBA low exposure terminology and proposed workflow

To enable informed selection of the EBA option and to facilitate the development of practical recommendations for documenting EBA justifications the ECETOC TF mapped all the current "low" exposure-based adaptation rules and pertinent REACH terminology in Table 7. It follows that two main EBA options are possible, namely, **qualitative and quantitative**.

For the qualitative approach the intent is to demonstrate low exposure solely using the information on uses and the measures implemented to prevent/minimise exposure and release. As such there is a requirement to identify uses where the potential for exposure is accepted to be low and document this. When employing a quantitative approach, the challenge is that with measured data or modelled exposure as long as some level of exposure is demonstrated it is not possible to state whether such exposure would be 'significant' or associated with some form of risk, particularly if there is no assessment of hazard potential. Therefore, in the event that a quantitative approach is employed, some comparison of exposure with a toxicity benchmark is necessary, and this is essentially the risk-based adaptation covered in the next section, Tier 2.

Table 7 "low" exposure-based adaptation rules and pertinent REACH terminology

Term	Reference REACH text	Type of assessment	Examples of criteria	Comments
No exposure	"Absence of exposure" in **Annex XI 3.2 (a)(i)** "No or no significant human exposure" **in Annex IX 8.7**	**Qualitative justification**. Mentioned in ECHA's Practical Guide 16 (PG16) on SCC (ECHA, 2014).	Closed systems, no emission Used in ECHA's PG16 (ECHA, 2014): "results of personal and static monitoring – all results below detection limits – confirm that no exposure via air occurs"	If there is no exposure, there is no hazard to be identified. Synonymous to "no relevant exposure". In PG16, associated with "no measured/detected exposure" for SCC (i.e., becomes quantitative).
No relevant exposure	Used **in Annex VIII 8.6.1 and 8.7.1** (relevant human exposure can be excluded in accordance with Annex XI section 3)	**Qualitative/quantitative** Not risk-based, i.e., does not consider hazard, only the absence of exposure for certain groups of population, or relevant routes of exposure.	Linked to types of uses (not to a level of exposure nor hazard): - e.g., no professionals use or no consumer use). - Workers: use in closed systems, low/minimised emissions… - physico-chemical properties or OC (Operational Conditions)s	When exposure is excluded the hazard identification and DNEL derivation are not necessary (no concern is expected). Even with a very hazardous substance, no adverse effects are expected in the absence of relevant ("significant") exposure. If human exposure is expected, the waiving is not possible.
Limited exposure	Used in **Annex IX 8.6.2**	**Quantitative exposure assessment; Risk-based**, i.e. RCR < 1 If exposure cannot be excluded then the risk must be negligible. syn: tolerable exposure	A low level, frequency, and/or duration, well-defined and small number of people, limited number of sites, combined with no evidence of systemic toxicity. Criteria associated with low absorption potential ("insoluble and not inhalable"), combined with no evidence of toxicity at 1000 mg/kg/d in a RDT limit test.	**Exposure assessment even when no hazard is identified** according to art.14 (4). (Note that in default REACH dossiers, when there is no evidence of toxicity at the limit dose, then DNEL is not necessary and no exposure assessment required)
No significant exposure	Used in **Annexes IX and X, 8.7, 8.7.3**. In **Annex XI 3.2(a)(i) and (iii)**, absence of exposure (i) and exposure well below the DNEL (iii)	**Quantitative exposure assessment** **Risk-based**, i.e. RCR < 1 (e.g. measurements, degree of exposure)	Very low level of exposure over a whole lifetime, or a single exposure at a specific occasion. (concentration and time, frequency)	**Exposure assessment even when no hazard is identified**). Limitation: "Well below the DNEL" is not clearly defined.

Term	Reference REACH text	Type of assessment	Examples of criteria	Comments
			Concerns substances with no evidence of toxicity in any of the tests available.	
Negligible exposure	Used in **Annex XI, 3.2(c)** (no release, negligible likelihood to be exposed)	**Qualitative/quantitative**	Low emissions, e.g., substance in article (matrix), or closed system or OC and RMM (Risk Management Measures) sufficient to avoid exposure (SCC)	Can be quantitative or qualitative, or semi-quantitative Can also use TTC. Workers, consumers (low concentration, or articles) Synonym of "acceptable"?
Minimised exposure	Used in Article 18.4 referenced in **Annex XI, 3.2(b)**	**Qualitative (exposure) assessment.** Minimise emissions and any resulting exposure by technical means.	Closed system and rigorous containment by technical means/RMM. Control of emissions by SCC.	

Qualitative approach

The key exposure determinants to be used for qualitative EBA of human health effects data include:

- The physico-chemical properties of a substance that characterise the likelihood of associated exposure. The following cut-off criteria may be considered indicative of low human systemic exposure:
    - Low fugacity (VP<0.01Pa for liquids, low dustiness for solids, no aerosol/particles generating processes or no fraction of the particle size distribution <100 µm (ECHA, 2017a).
    - Low bioavailability (i.e. unlikeliness to be absorbed or cross biological barrier) with MW>800 or molecular diameter > 17 Å and logKow <-1 or >4 (Marquart et al., 2012; OECD, 2011; OECD, 2019; ECHA, 2017c; ECHA 2017d; Matsson and Kihlberg, 2017) (excluding pesticides; EFSA, Buist et al., 2017), insolubility in water and/or biological fluids (e.g. solubility < 1 mg/L) (Marquart et al., 2012);
    - Other relevant inherent properties preventing certain adverse systemic effects and serve to limit exposure, e.g. corrosion/ sensitisation, non-reactiveness.
- The type of use, including operational conditions and risk management measures in place. The associated criteria are largely based on the requirements already in place for demonstrating SCCs and no release from articles (Table 8).

Table 8: Criteria for demonstrating SCCs and no release from articles

Strictly Controled Conditions	**No release from articles**
Manufacture and industrial intermediate uses only (no professional or consumer uses). Check for PROCs (and ERCs) descriptors that are not compatible with SCCs (see ECHA's REACH guidance on intermediates, 2010)	Low concentration in products (e.g. concentration <0.1%)
Exposure is avoided primarily by technical means (e.g. closed system with limited breaches, rigorous containment by engineered controls, control of emissions to the environment) and organisational measures where appropriate See examples of detailed technical measures in Annex 7B of the Commission Directive 2001/59/EC (28th ATP) (European Commission, 2001), and Illustrative practical examples of technical means in UIC / SICOS guidance (in french) (UIC / SICOS, 2017).	Evidence of no significant unbound residual amount in a matrix and that covalent binding remains stable (i.e. encapsulation effect using e.g., transmission electron microscopy (**TEM**) techniques)
Automated continuous (not batch) processes, restricted entry	
Short term (acute) exposures and/or low use frequency	

Strictly Controled Conditions	**No release from articles**
Documented proof of no exposure, e.g. workplace exposure modelling or monitoring and/or bio-monitoring (if available) ≤ LOD for the majority of samples (Practical Guide 16, ECHA, 2014). Alternatively it could be < 0.1OEL if OEL exists. Note: the LOD must be sufficiently low, e.g. in the range of TTC levels in the absence of reliable DNEL (see the Risk based approach document)	Documented proof of no exposure/release, e.g. using migration modelling, results from standardised leaching/bioelution tests (if available) ≤ LOD. Note: the LOD must be sufficiently low, e.g. in the range of TTC levels in the absence of reliable DNEL (see the Risk based approach document)

The strictly controlled conditions of use for intermediates (ECHA, 2010) represent a useful benchmark against which to judge qualitative EBA justifications. A more detailed list of key elements worth consideration when compiling the SCC-based EBA documentation can be found in Appendix I. It should be noted that in the context of intermediates under SCC registration, “no exposure” evidence is required not only for workers but the environment too. Thus, for EBA of human endpoints, data for the environment may be needed as well.

Notably, the expectation to provide monitoring/measured data as a documented proof of no (residual) release and resulted exposure that may occur despite of rigorous containment measures by technical means is debatable. In practice, an industrial exposure dataset is collected for a specific scenario of interest (e.g. tasks with potentially high exposure) and cannot be considered representative of typical/mean or low occupational exposure, the likelihood and magnitude of which are pre-determined and de-prioritised by initial expert judgement based on the implemented controls.

Same is true for the “no release from articles” scenario: measured data obtained for e.g. a monomer in polymer may not be representative of the release potential outcome for the finished plastic article. Often times, substance registrants simply do not have access to the products safety testing data generated downstream. Therefore, conclusions derived using validated exposure modelling tools should be deemed acceptable.

Tier 2: Risk Based approach

The proposal for a risk-based approach to adapting data requirements is a refinement of that currently written in Annex XI, section 3 of the REACH legal text. The intent is to make this approach more feasible without compromising a high level of human and environmental protection.

The existing provisions for using a risk-based adaptation in Annex XI, section 3 are:

a. the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate no or no significant exposure in all scenarios of the manufacture and all identified uses;
b. a DNEL can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes. However:
    i. a DNEL derived from a screening test for reproductive/developmental toxicity is not considered appropriate to omit a prenatal developmental toxicity study or a two-generation/extended one generation reproductive toxicity study.
    ii. a DNEL derived from a 28-day repeated dose toxicity study is not considered appropriate to omit a 90-day repeated dose toxicity study.
c. the comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL;

In this proposed risk-based approach to adapting data requirements in Annexes VIII – X, toxicity studies can be waived based on the fact that the risk assessment covering all relevant exposures throughout the life cycle of the substance demonstrate that no adverse health effects will result from any exposure scenarios. In other words, all exposures should be below the DNEL derived from the available data. This means that, based on the current state of the art, it is unlikely that the results of the study to be waived would modify the conclusion of the chemical safety assessment.

Unlike the existing Annex XI adaptation where one must demonstrate no or no significant exposure and where there are limitations placed on the data forming the basis of a DNEL, for this proposed adaptation the requirements have been harmonised with what is expected for conventional registrations for lower tonnage band (and thus 'lower exposure potential') substances. As such, there is no requirement to demonstrate no or no significant exposure. Rather a suitably derived DNEL and a comprehensive exposure and risk assessment is required, the nature of which will be determined by the available data. The options for quantifying exposure are discussed elsewhere, here we address the

quantification of hazard (=DNEL), based on available data other than the study to be waived and the risk assessment itself.

Hazard Characterisation

In order to perform the risk assessment a DNEL or other toxicity benchmark is necessary. To derive this benchmark three different situations can be discerned:

1. There are lower tier (Annex VIII) repeated dose studies available for the same endpoint
2. There are only repeated dose studies available addressing a different endpoint
3. There are no repeated dose studies available

Irrespective of the scenario it should be recognised that for the purposes of a risk assessment assessing potential repeated exposure, any repeated dose toxicity data of sufficient quality can be used to derive a toxicity benchmark as long as uncertainty in the hazard characterisation is adequately addressed. For example, at the tonnage band 10-100t, only a 28-day and reproductive screening study (or the combined study) are required under REACH. If a substance is classified as hazardous and the risk assessment of identified uses is triggered, the data from these studies is adequate to form the basis of the DNELs. The standard assessment factors utilised in this situation include extrapolation from animals to humans, human variability, and time extrapolation. Additional factors including the quality of the database and severity of the dose response can be applied if deemed appropriate. Therefore, when considering which data can be used to form the basis of a toxicity benchmark it is important to recognise that there is no robust scientific basis for excluding certain study types as long as uncertainty is addressed adequately.

It is therefore proposed that for the risk-based adaptation, any good quality repeated dose toxicity data can be used to derive a DNEL for the related endpoint. However, it is recognised that there is a need to address potential uncertainty in this approach when deriving the DNEL and this is discussed further below.

Studies available addressing the same endpoint

This case will mainly concern the situation where a DNEL is derived using repeated dose toxicity studies of a shorter exposure duration than the study to be waived. In this scenario the potential sources of uncertainty come from the unknown impact of exposure duration on toxicity as well as differences in the study designs, including animal numbers and the endpoints addressed within the study design. For substances not easily cleared from the body, longer term studies allow for potential accumulation of the substance or saturation of defence mechanisms of the test system which may trigger adverse

effects not observed in shorter duration studies. In longer term studies such as a 90-day repeated dose study, there are typically additional observations such as a functional observational battery (FOB) which are not included in the 28-day study protocol. The longer duration studies (>60 days) also cover an entire spermatogenic cycle which allows for a more comprehensive assessment of male reproductive organs.

At the 10-100t level which only requires these shorter duration studies, the uncertainty associated with having a shorter term study is addressed during DNEL derivation using an exposure duration extrapolation factor. These factors are based on the median of distribution of the proportion of the NOAELs derived from shorter and longer-term animal toxicity studies (Escher et al., 2020). This assessment therefore takes into consideration not only how the study duration affects toxicity, but also the different sensitivity of the study types. In principle, this time extrapolation factor should be sufficient for addressing uncertainty when deriving the DNEL in support of a risk-based adaptation.

However, if there was higher uncertainty in the risk assessment due to e.g. a complex value chain with a large number of uses, or when the bioaccumulation assessment is based on less reliable information, a more conservative cut-off, e.g. the 90th percentile could be chosen. To determine this cut-off, a reanalysis of the data used to determine the above assessment factors, based on a database including recent studies, could be applied.

Studies available addressing a different endpoint

Where repeated dose toxicity studies are available (for example, 28-day, 90-day and combined repeated dose/reproductive screening studies), the effect levels from these can be used to derive a DNEL to adapt the requirement for developmental and higher tier reproductive studies. In this scenario, the main source of uncertainty is the difference in endpoint. Although the repeated dose studies such as 28-day and 90-day studies can provide some insight into the potential toxicity to sex organs, they are not able to assess reproductive functioning and provide no information on potential developmental toxicity. Similarly, the reproductive screening study provides information on fertility and development but is not as sensitive as the extended one generation and developmental toxicity studies. As with the first scenario, for lower tonnage substances with lower data requirements, there is no standard practice when deriving a DNEL to consider factors other than time extrapolation. i.e. it is not typical that additional factors are applied to address the uncertainty that higher tier studies are not available. Therefore, it can be argued it is not justified to include an additional assessment factor to account for additional uncertainty by default. However, an additional factor could be used where appropriate, for example where there is a concern that the substance may have reproductive and/or

developmental effects (based on data from similar substances). When considering the need for a further assessment factor, it should be noted that there are multiple publications comparing general toxicity points of departure to those from developmental studies, concluding that developmental toxicity was not a more sensitive endpoint for risk characterisation purposes than other non-cancer endpoints (Kroes et al., 2004; Bernauer et al., 2008; Melching-Kollmuß et al., 2010; Laufersweiler et al., 2012 and van Ravenzwaay et al., 2017). This would suggest that using an additional uncertainty factor to account for a difference in endpoint is likely to be unnecessary.However a robust database with NOAELs of general toxicity studies, developmental toxicity studies and generation studies should be established and the distribution of their proportion for relevant combinations of studies analysed. Using an appropriate cut-off, e.g. the 90th percentile, an extrapolation factor could determined for, e.g., a 90-day study to a developmental toxicity study.

No repeated dosing studies available

For substances with very low exposure potential and no repeated dose toxicity data, an approach which could be appropriate here is a Threshold of Toxicological concern approach, in which the TTC takes the place of the DNEL.

The threshold of toxicological concern (TTC) approach is a screening tool that has been developed in order to assess substances of unknown toxicity present at low levels in the diet (Kroes et al., 2004). Application of the TTC approach requires only knowledge of the chemical structure of the substance concerned on human exposure, for which there is confidence that it is not an underestimate. It utilises generic human exposure threshold values (also called TTC values) that have been established for substances grouped according to their chemical structure and likelihood of toxicity. Since the concept cannot be applied to all chemical structures, e.g. inorganics and dioxins are excluded and should be covered by a chemical specific assessment (see e.g. Kroes et al., 2004; EFSA, 2012; EFSA and WHO, 2016), it is imperative to know the structural identity of the chemicals to be evaluated. This introduces a challenge for ill-defined substances such as UVCBs. The latest guidance on the use of (oral) TTC is given by the European Food Safety Authority (EFSA, More et al., 2019). TTC levels are specified in the tables below.

Oral TTC values for consumers (EFSA, More et al., 2019)

Chemical class	**µg/person/d**	**µg/kg bw/d**
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3

Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1,800	30

Respiratory TTC values normalised for consumers (Escher et al., 2010)

Chemical class	**TTC values[a]**		
	ppm	**mg/m³**	**µg/person/d**
Cramer Class I	3.6×10^{-3}	8.9×10^{-3}	180
Cramer Class III	2.4×10^{-5}	1.8×10^{-4}	4

[a] Excluding genotoxic chemicals

The values given by Escher et al. were normalised for consumers (i.e. 24 hours/day, 7 days/week) and thus need to be adjusted when used for worker exposure scenarios (see table below).

Respiratory TTC values normalised for workers (derived from Escher et al., 2010)

Chemical class	**TTC values[a]**		
	ppm[b]	**mg/m³ [b]**	**µg/person/d[c]**
Cramer Class I	3.0×10^{-2}	7.5×10^{-2}	750
Cramer Class III	2.0×10^{-4}	1.5×10^{-3}	15

[a] Excluding genotoxic chemicals

[b] Calculated from consumer values by reducing daily exposure from 24 h to 8 h, weekly exposure from 7 to 5 days and using an intraspecies extrapolation factor of 5 instead of 10 (see ECHA, 2012b)

[c] Calculated from the mass per volume TTC by multiplication with the default daily worker respiratory volume of 10 m^3 (ECHA, 2012b)

There are no dermal TTC values based on a database of dermal toxicity studies. Therefore, it is proposed to apply the oral values, assuming equal dermal and oral absorption, which can be considered a worst case.

It should be noted that the TTC levels specified here are quite low and can only be used for exposure-based waiving, provided exposure assessment methods available are sensitive enough to prove that

the very low levels of exposure associated with the various TTC levels are not exceeded. For genotoxic chemicals a TTC approach will not be feasible as this level of exposure (only available for the oral route) is too low to be measured with the current state-of-the art exposure measurement or modelling approaches.

Recommendation for appropriate studies for DNEL derivation

Taking into consideration the above and the identified uncertainty, if the intent is to adapt the data requirements listed in Annexes IX and X, it is recommended to address the data requirements for the 28-day and reproductive screening study and to use these studies to derive a DNEL. If such data do not exist, it is recommended to perform the combined study (OECD 422) and in doing so, one can consider whether the study design can be modified to include elements such as a toxicokinetics add-on to assess bioaccumulation, an extended pre-mating exposure period, functional/observational battery, larger size dose groups, etc. to reduce uncertainty in the final DNEL derivation.

If the intent is to waive all repeated dose and reproductive/developmental studies in annexes VIII, IX and X using EBA, this would only be possible using either a qualitative low exposure approach as specified in the 'Low exposure' proposal, or by using a risk-based approach which utilises an alternative toxicity benchmark to the DNEL such as the TTC.

Exposure assessment

A pragmatic tiered approach to exposure assessment is suggested. The starting point is to model worker and consumer exposure using Tier 1 ECETOC TRA v.3.1 tool taking a full account of any hazard classification mandating specific risk management measures (e.g. gloves for classified skin irritants), the actual sector-specific OCs and RMMs (if available, e.g. Generic Exposure Scenarios for industrial, SWEDs (Specific Worker Exposure Determinants) for professional and SCEDs (Specific Consumer Exposure Determinants) for consumer uses) or assuming basic/minimal RMMs in place for non-classified substances.

Specifically, the utility of personal protective equipment in controlling worker exposure can be justified only for short term and/or infrequent exposures (e.g. sampling, cleaning and maintenance), but should be not relied upon as a routine measure. Ideally, exposure assessment should address variability in possible OCs and RMMs (e.g. different operating temperatures, indoor and outdoor use) for specific contributing scenarios. For consumers, additional exposure limiting factors, such as low concentration in products, packaging designed to minimise or limit inappropriate exposure, could be considered.

Overall, justification of measures and assumptions used to reduce/manage exposures will have to be sufficiently detailed and (ideally) supported by published data.

On the basis of the Tier 1 assessment results, a (limited) number of contributing scenarios may be identified, for which higher tier assessment (using models or measured data) will be warranted to gain higher level of confidence in predicted exposures. More detail on that step is provided in Appendix II. Proceeding to a higher tier exposure assessment will be driven by the RCRs resulted from comparison of Tier 1 exposure predictions to (long-term) systemic DNEL(s) derived specifically for EBA purposes.

For the EBA-oriented exposure assessments, in particular, it is critical that the predicted low exposures are not underestimated. Numerous research studies indicate that the distance between predicted and measured exposure varies significantly depending on the PROC/PCs (Hesse et al., 2015; Franken et al., 2020; Schlueter et al., 2020). Uncertainty in the exposure assessment can therefore be reduced by comparing the estimates from a range of sources, including different tools and measured data. Given the uncertainty inherent in many exposure assessment tools, RCRs close to 1 may rather indicate that further investigation is necessary, e.g. further iteration within the tool or assessment by other means. Use of single tool estimates is unlikely to be persuasive enough for the purposes of assessing circumstances related to strictly controlled conditions or for proving the low level exposures demanded by risk-based adaptations.

Finally, the assessment of human exposure via the environment should not be forgotten for higher tonnage substances (> 100 t/y). It is mandatory at tonnage above 1000 t/y for all hazardous substances. However, at tonnages above 100 t/y, the requirement depends on the hazard classification: it applies to substances classified as STOT RE1, or as carcinogen or mutagen (categories 1 or 2), or as toxic to reproduction (categories 1A or 1B). In case of EBA justification, ‘man via environment’ should generally be taken into consideration.

Should some uses be restricted?

As stated above this proposal does not mandate that there should be no or no significant exposure since the basis for whether the adaptation is valid rests on the risk assessment outcome. However, it is recognised that not all uses are equal as far as exposure is concerned therefore it is considered whether it is necessary to limit the use of a risk based adaptation to substances with uses with more limited exposure potential e.g. “not wide-spread use” or “industrial / professional use only”. However, exposures at workplaces are typically much higher than consumer exposures. In addition, by the application of a larger uncertainty factor in the extrapolation to obtain a DNEL or the conservatisms of the TTC approach, exposure already has to be quite low to meet the criteria for safe use under

conditions of exposure-based waiving. Furthermore, if any exposure scenario considered for the substance under scrutiny results in exceedance of the reference value, exposure-based waving will not be suitable, and more information will need to be generated. Therefore, it is not deemed necessary to restrict risk-based exposure-based waiving to specific exposure scenarios since the approach will be self-limiting.

Risk assessment outcome

According to Annex XI.3.2.a. it is currently stated that the RCR should be **well below 1** for exposure-based adaptation using the risk assessment approach, however no quantification is given. If the above proposal of an additional data-based assessment factor to address uncertainty coming from the absence of higher tier studies is followed, then the need to stay "well below the DNEL" is void, as the uncertainty associated with this adaptation has already been compensated for in the DNEL derivation and by a conservative exposure assessment. Therefore, it is proposed that the risk assessment outcome of an RCR <1 is acceptable for the purposes of an exposure-based adaptation.

Classification and labelling

In absence of specific higher tier studies (such as developmental or multi-generation reproductive studies), the data would not be available to definitively conclude on classification for these endpoints. However, the same potential issue exists for substances registered at a lower tonnage band. It is proposed that in the presence of a reproductive toxicity screening study no labelling is necessary when no adverse (reprotoxic) effects were seen at the limit dose. If potentially classifiable effects were seen, the actions to be taken should be consistent with what is required of substances registered in a lower tonnage band; for example a test proposal, a labelling proposal or still a proposal not to label, depending on specific circumstances (e.g. strictly controlled or wide-spread use, but also other non-scientific considerations (economic, intended use (professional or consumer), etc.). It is noteworthy that hazard classification in itself is a useful tool to communicate hazards along the value chain, however, it is only a supporting element of chemical risk management. Only adherence to supported or self-assessed uses with the specified exposure controls, based on relevant DNELs can minimise risks. Knowledge of hazard class is not a condition for safe use of chemicals.

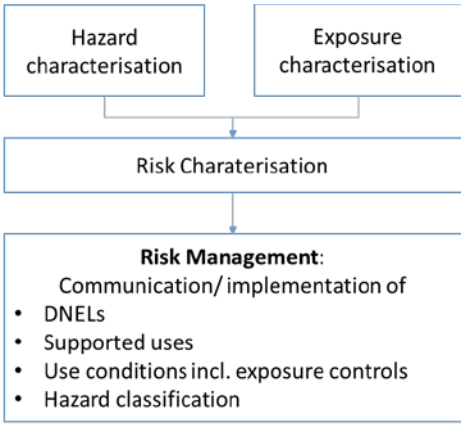

Figure 1 : Elements of risk management

Summary

The key elements of this proposed approach are:

- No a priori requirement that there be no or no significant exposure
- No limitation of which studies can be used to form a DNEL as long as the studies are of good quality and reliable.
- Use of adequate assessment factors to account for uncertainty, potentially including an additional factor to address uncertainty specific to the use of the exposure-based adaptation
- The risk assessment outcome should be an RCR<1

Appendix I

Table I-1. Short list / Examples of key elements to address during the qualitative EBA type review:

Key elements	**Examples of the highest control levels to minimise emissions**
Substance related:	
Physical form(s)	Solid, powder, liquid
Physico-chemical properties	Vapour pressure, solubility, particle size…
Types of uses	Products, market, use concentrations
Technical measures:	
Type of process	Continuous process (typically better than batch process with transfers)
Transfers	Filling lines equipped with dry break couplings ; vapour return system; purging of lines after filling
Equipment	Fully automated and closed system, leakproof, remotely controlled system; rigorous containment, segregation of the emitting process
Level of containment	Multiple layers of process containment (sealed process in secondary container)
Breaching incidents	No breaching of containment during containment, or no direct operator activity
Leakage prevention	System with negative pressure (pressure monitoring), fitted enclosures (secondary envelope), leakproofness inspections, sensors at critical points with alarms to ensure the absence of substance
Treatment of contaminated air	Integrated highly effective exhaust ventilation; Exhausted air cleaned by backed-up high efficiency abatement system outside the building; back-flow prevention
Cleaning and Maintenance	Filtration system backed up by a second system regularly certified and checked. Special procedures including purging and washing before the system is opened and entered.
Level of contact	No direct contact. Transfers automated and controlled remotely in an enclosed process
Recovery and management of waste	Incineration of exhaust air and waste waters
Organisational measures:	
Risk management measures	Minimisation of manual operations, avoidance of contact with contaminated surfaces (tools, objects); Management system in place identifying roles of the individuals in the organisation
Cleaning	regular cleaning of equipment and work area
Training	training of personnel to OC and RMM and PPE (Personal Protection Equipment)
Good practices	management supervision, good practices, personal hygiene, housekeeping
Procedures	Procedures to minimise residual emissions from rigorous containment Procedures and training for emergency decontamination and disposal
Supporting considerations:	

Key elements	**Examples of the highest control levels to minimise emissions**
Intensity of use	Frequency, duration of use and activities that can influence the exposure level. - low amounts used per day, - low concentration in process, and/or final product(s) - unlikely contacts, - few transfer operations during production. - Limited number of sites, - limited number of workers involved, - low use frequency
Uncertainties	Describe major uncertainties
Supporting monitoring data	When available measured exposure data can be included. Air monitoring is not indicated as a requirement, but "can be used to help to demonstrate strict control" (Practical Guide 16, ECHA, 2014) Exposure estimations using modelling or measured data, or appropriate analogous/surrogate data can be provided (Practical Guide 15, ECHA, 2012c)

Appendix II

A chemical placed on the European market at volumes > 1tonne/year should be first registered under REACH by its manufacturer or importer. An essential part of the registration dossier is the description of identified uses for the substance; it usually starts with Manufacture and/or Formulation or Re-packing, and may comprise a number of industrial, professional and/or consumer end-uses. Therefore, it is appropriate to expect that any type of EBA pursued under section 3.2 of REACH Annex XI (i.e. 3.2(a, b or c)) will need a thorough and rigorous worker exposure assessment to address (at a minimum) Manufacture and/or Formulation or Re-packing life cycle stages.

Existing REACH guidance on worker exposure assessment Chapter R.14 (ECHA, 2016a) describes in detail the considerations important for evaluation of occupational exposure to chemicals; it also lists several exposure assessment approaches with respect to their strengths and limitations, providing recommendations as to how they can be applied for developing REACH CSAs. One of the key aspects worth noting here, is that in line with the tiered approach strategy generally recommended for any kind of exposure assessment (Meek et al., 2011; Embry et al., 2014), a pragmatic workflow here would be to start with Tier 1 exposure modelling. Then, on the basis of the Tier 1 assessment results, a (limited) number of contributing scenarios could be identified, for which either higher tier modelling or measured exposure data would be needed.

It is important to recognise that the purpose of EBA-oriented exposure assessment is fundamentally different from that carried out in a frame of standard REACH CSA. In the latter, the focus is on the derivation of appropriate Risk Management Measures (RMMs) and Operational Conditions (OCs) which are to be communicated down the supply chain to ensure safe use. These should be generally aligned and consistent with the hazards identified in the initial step of the risk assessment. Hence, when no hazard has been identified, no DNEL are derived and no exposure assessment is needed.

In contrast, in the context of EBA, even though there is no evidence of toxicity (or potential hazards may be unknown due to missing studies) a thorough and rigorous exposure assessment is required in accordance with section 5 of REACH Annex I, i.e. exposure scenarios need to be developed. Exposure scenarios should be attached to the Chemical Safety Report, which poses technical challenges for setting up and exporting IUCLID file into ECHA's chemical safety assessment and reporting tool (Chesar) for non-classified substances.

Considering a different scope and objectives of EBA-oriented exposure assessment, it is argued that the format of EBA-tailored exposure scenarios may differ from those required for CSR and extended SDS. As mentioned in REACH Annex I Section 0.8 the level of detail required in describing an exposure scenario can vary substantially from case to case, and may describe the appropriate risk management measures for several individual processes or uses of a substance. An EBA-tailored exposure scenario may thereby cover a large range of processes/activities that are typical/common for various uses across the entire chemical life cycle. Such a format allows to avoid repetition and facilitates ECHA's review.

Exposure assessment for EBA will then capture the true/actual human exposure occurring in reality, taking a full account of any existing hazard classification mandating specific risk management measures, the actual sector-specific RMMs and OCs or assuming basic/minimal RMMs in place for non-classified substances. It is reasonable to expect that EBA justifications will be mainly developed for waiving of long-term repeated exposure animal studies (e.g. sub-chronic repeated dose, extended one

generation reproductive toxicity, prenatal developmental toxicity testing), hence, it is generally the chronic systemic exposure that will need to be evaluated in detail.

The ECETOC EBA Task Force has evaluated several human exposure models commonly used REACH and developed recommendations as to what a thorough and rigorous exposure assessment for EBA might constitute and how it could be prepared in an efficient manner. For worker exposure the models evaluated included ECETOC TRA v.3.1, Stoffenmanager v.4.5 and Advanced Reach Tool (ART) v.1.5[5]. Other models, e.g. MEASE, Easy-TRA, EMKG, BEAT, were not considered here. For consumers, we addressed ECETOC TRA v.3.1, ESIG EGRET v.2.0[6], and ConsExpo v.4.1.

The evaluated models differ in complexity with respect to input data requirements and embedded algorithms for calculation of exposure, and hence represent different tiers of exposure modelling, with the ECETOC TRA being considered a Tier 1 REACH tool. The tools are intended to provide appropriately conservative estimates when used correctly. Like any other model, exposure estimation tools have limitations with respect to their applicability domain, such as the scope of the intended use or physico-chemical properties of the substances. Users are required to ensure that the assessment is within the applicability domain of the models (see ECHA, 2016a and 2016b).

Tier 1 REACH exposure assessment for EBA.

The starting point is to model worker and consumer exposure using Tier 1 ECETOC TRA v.3.1 tool taking a full account of any health hazard classification mandating specific risk management measures (e.g. gloves for classified skin irritants), the actual sector-specific RMMs and OCs communicated in REACH exposure scenarios built on e.g. GES, SWEDs and SCEDs[7], or assuming basic/minimal RMMs in place for non-classified substances.

Tables II-1 and II-2 enable rapid mapping of TRA-based worker and consumer exposure, respectively, predicted **for a pure liquid substance of MW=200 g/mole**. Such a mapping allows instant view on the lowest possible worker exposure predicted by the TRA tool. They provide an overview of exposure ranges covered by different models for various scenario settings to facilitate a quick selection of the most suitable tool for EBA for the substance in question.

For workers, the predictions were developed for the main work process categories (PROCs) with and without typical RMMs encountered at industrial and professional workplaces ; the data on sector-specific RMMs can be found in ECHA's use map library (link[8]). Different volatility bands were examined. The exposures can be easily recalculated using default exposure modifying factors (ECETOC, 2014) for substances with different MW and vapor pressure, reduced concentration in a mixture and/or alternative RMMs, if needed. Figure II-1 provides visualization of worker exposure estimates in Table II-1.

For consumers, the default TRA v.3.1 exposure estimates for a substance with MW=200 g/mole and VP=10 Pa are accompanied with more refined exposure predictions obtained using SCEDs data (where

[5] Stoffenmanager, now available as version 8, and can be used to predict inhalation exposure to non-volatile liquids and powders. ART is a higher tier inhalation worker exposure model. The tool incorporates a database of exposure measurements, including data from handling low-volatility liquids, solid objects, and powders, granules, or pelletized material. These data can be used in conjunction with mechanistically derived exposure estimates within the tool.

[6] ESIG EGRET – the European Industry Solvents Group (ESIG) GES Risk and Exposure Tool https://www.esig.org/reach-ges/consumers/

[7] GES – ESIG Generic Exposure Scenarios available at https://www.esig.org/reach-ges/
SWEDs – Sector specific Worker Exposure Descriptions available at https://echa.europa.eu/csr-es-roadmap/use-maps/use-maps-library
SCEDs – Specific Consumer Exposure Determinants available at https://echa.europa.eu/csr-es-roadmap/use-maps/use-maps-library

[8] https://echa.europa.eu/csr-es-roadmap/use-maps/use-maps-library

available in ECHA's use map library) and the ESIG EGRET v.2.0 model. Table II-2 contains estimates for daily inhalation, dermal and oral consumer exposure for a wide range of product categories (PC) and article categories (AC) typically covered in REACH registrations. In the case of TRA+SCEDs, the daily exposure calculations for the (PCs) scenarios with shorter than 24 hours exposure duration were adjusted following the algorithm proposed in ECHA's IR&CSR Guidance Chapter R.15 (ECHA, 2016). EGRET daily exposure estimates were derived using the embedded algorithm (i.e. averaging the event exposures over 24 hours). No adjustment was made for the (in)frequency of consumer use of any PC evaluated. Similarly to workers, consumer exposure estimates in Table II-2 s can be recalculated for different MW and/or lower vapor pressure, using the corresponding exposure modifying factor to account for the decreased "fraction released to air" (ECETOC, 2009). Figures II-2 and II-3 visualize the consumer exposure assessment results from Table II-2.

Table II-1. Tier 1 REACH Worker exposure assessment results using ECETOC TRA v.3.0 model. Values in the same fugacity band represent ranges of predicted exposure for a hypothetical liquid substance (MW=200g/mole) in a pure form; for MW=X exposure values need to be multiplied by X/200.

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Ind	PROC1	1 - Use in closed process, no likelihood of exposure	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	3.00E-02	3.00E-04
Ind	PROC2	2 - Use in closed, continuous process with occasional controlled exposure	7.50E+00	8.33E+00	2.25E-03	2.50E-03	4.17E+01	1.25E-02	2.08E+02	6.25E-02	1.37E+00	1.37E-02
Ind	PROC2	2 - Use in closed, continuous process with occasional controlled exposure **at elevated temperature**	4.17E+01	4.17E+01	1.25E-02	1.25E-02	2.08E+02	6.25E-02	2.08E+02	6.25E-02	1.37E+00	1.37E-02
Ind	PROC3	3 - Use in closed batch process (synthesis or formulation)	2.50E+01	2.50E+01	7.50E-03	7.50E-03	8.33E+01	2.50E-02	4.17E+02	1.25E-01	6.90E-01	6.90E-03
Ind	PROC3	3 - Use in closed batch process (synthesis or formulation) **at elevated temperature**	8.33E+01	8.33E+01	2.50E-02	2.50E-02	4.17E+02	1.25E-01	4.17E+02	1.25E-01	6.90E-01	6.90E-03

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Ind	PROC4	4 - Use in batch and other process (synthesis) where opportunity for exposure arises	4.17E+01	4.17E+01	1.25E-02	1.25E-02	1.67E+02	5.00E-02	8.33E+02	2.50E-01	6.86E+00	6.86E-02
Ind	PROC4	4 - Use in batch and other process (synthesis) where opportunity for exposure arises **at elevated temperature**	1.67E+02	1.67E+02	5.00E-02	5.00E-02	8.33E+02	2.50E-01	8.33E+02	2.50E-01	6.86E+00	6.86E-02
Ind	PROC5	5 -Mixing or blending in batch processes (multistage and/or significant contact)	4.17E+01	4.17E+01	1.25E-02	1.25E-02	4.17E+02	1.25E-01	2.08E+03	6.25E-01	1.37E+01	1.37E-01
Ind	PROC6	6 -Calendering operations	4.17E+01	4.17E+01	1.25E-02	1.25E-02	4.17E+02	1.25E-01	2.08E+03	6.25E-01	2.74E+01	2.74E-01
Ind	PROC7	7 -Industrial spraying	8.25E+02	8.33E+02	1.24E-01	1.25E-01	2.08E+03	3.13E-01	4.17E+03	6.25E-01	4.29E+01	2.14E-02
Ind	PROC8a	8a -Transfer of chemicals from/to vessels/ large containers at non dedicated facilities	7.50E+01	8.33E+01	2.25E-02	2.50E-02	4.17E+02	1.25E-01	2.08E+03	6.25E-01	1.37E+01	1.37E-01
Ind	PROC8b	8b -Transfer of chemicals from/to vessels/ large containers at dedicated facilities	5.00E+01	4.17E+01	7.50E-03	6.25E-03	2.08E+02	3.13E-02	1.25E+03	1.88E-01	1.37E+01	1.37E-01

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Ind	PROC8b	8b -Transfer of chemicals from/to vessels/ large containers at dedicated facilities **at elevated temperature**	2.08E+02	2.08E+02	3.13E-02	3.13E-02	1.25E+03	1.88E-01	1.25E+03	1.88E-01	1.37E+01	1.37E-01
Ind	PROC9	9 -Transfer of chemicals into small containers (dedicated filling line)	4.17E+01	4.17E+01	1.25E-02	1.25E-02	4.17E+02	1.25E-01	1.67E+03	5.00E-01	6.86E+00	6.86E-02
Ind	PROC10	10 - Roller application or brushing	7.50E+01	8.33E+01	2.25E-02	2.50E-02	4.17E+02	1.25E-01	2.08E+03	6.25E-01	2.74E+01	2.74E-01
Ind	PROC11	11 - Non industrial spraying	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	NA	NA
Ind	PROC12	12 - Use of blow agents for foam production	1.67E+01	1.67E+01	5.00E-03	5.00E-03	1.67E+02	5.00E-02	8.33E+02	2.50E-01	3.40E-01	3.40E-03
Ind	PROC13	13 -Treatment of articles by dipping and pouring	7.50E+01	8.33E+01	2.25E-02	2.50E-02	4.17E+02	1.25E-01	2.08E+03	6.25E-01	1.37E+01	1.37E-01
Ind	PROC14	14 - Production of preparations or articles by tabletting, compression, extrusion, pelletisation	4.17E+01	4.17E+01	1.25E-02	1.25E-02	4.17E+02	1.25E-01	2.08E+03	6.25E-01	3.43E+00	3.43E-02
Ind	PROC15	15 - Use of laboratory reagents in small scale laboratories	3.33E+01	4.17E+01	1.00E-02	1.25E-02	8.33E+01	2.50E-02	4.17E+02	1.25E-01	3.40E-01	3.40E-03
Ind	PROC16	16 - Using material as fuel sources, limited exposure to unburned product to be expected	7.50E+00	8.33E+00	2.25E-03	2.50E-03	4.17E+01	1.25E-02	2.08E+02	6.25E-02	3.40E-01	3.40E-03

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Ind	PROC17	17 - Lubrication at high energy conditions and in partly open process	1.67E+02	1.67E+02	5.00E-02	5.00E-02	4.17E+02	1.25E-01	8.33E+02	2.50E-01	2.74E+01	2.74E-02
Ind	PROC17	17 - Lubrication at high energy conditions and in partly open process **at elevated temperature**	4.17E+02	4.17E+02	1.25E-01	1.25E-01	8.33E+02	2.50E-01	8.33E+02	2.50E-01	2.74E+01	2.74E-02
Ind	PROC18	18 - Greasing at high energy conditions	1.67E+02	1.67E+02	5.00E-02	5.00E-02	4.17E+02	1.25E-01	8.33E+02	2.50E-01	1.37E+01	1.37E-02
Ind	PROC19***	19 - Hand-mixing with intimate contact (only PPE available)	7.50E+01	8.33E+01	2.25E-01	2.50E-01	4.17E+02	1.25E+00	2.08E+03	6.25E+00	1.41E+02	1.41E+00
Ind	PROC20	20 - Heat and pressure transfer fluids (closed systems) in dispersive use	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	1.71E+00	1.71E-02
Prof	PROC1	1 - Use in closed process, no likelihood of exposure	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	8.33E-02	3.00E-02	6.00E-04
Prof	PROC2	2 - Use in closed, continuous process with occasional controlled exposure	4.17E+01	4.17E+01	1.17E-01	1.17E-01	1.67E+02	4.67E-01	4.17E+02	1.17E+00	1.37E+00	2.74E-02
Prof	PROC2	2 - Use in closed, continuous process with occasional controlled exposure **at elevated temperature**	1.67E+02	1.67E+02	4.67E-01	4.67E-01	4.17E+02	1.17E+00	4.17E+02	1.17E+00	1.37E+00	2.74E-02

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Prof	PROC3	3 - Use in closed batch process (synthesis or formulation)	2.50E+01	2.50E+01	7.00E-02	7.00E-02	2.08E+02	5.83E-01	8.33E+02	2.33E+00	6.90E-01	1.38E-02
Prof	PROC3	3 - Use in closed batch process (synthesis or formulation) **at elevated temperature**	2.08E+02	2.08E+02	5.83E-01	5.83E-01	8.33E+02	2.33E+00	8.33E+02	2.33E+00	6.90E-01	1.38E-02
Prof	PROC4	4 - Use in batch and other process (synthesis) where opportunity for exposure arises	7.50E+01	8.33E+01	2.10E-01	2.33E-01	4.17E+02	1.17E+00	2.08E+03	5.83E+00	6.86E+00	1.37E-01
Prof	PROC4	4 - Use in batch and other process (synthesis) where opportunity for exposure arises **at elevated temperature**	4.17E+02	4.17E+02	1.17E+00	1.17E+00	2.08E+03	5.83E+00	2.08E+03	5.83E+00	6.86E+00	1.37E-01
Prof	PROC5	5 -Mixing or blending in batch processes (multistage and/or significant contact)	8.33E+01	8.33E+01	2.33E-01	2.33E-01	8.33E+02	2.33E+00	4.17E+03	1.17E+01	1.37E+01	2.74E-01
Prof	PROC6	6 -Calendering operations	8.33E+01	8.33E+01	2.33E-01	2.33E-01	8.33E+02	2.33E+00	4.17E+03	1.17E+01	2.74E+01	5.49E-01
Prof	PROC7	7 -Industrial spraying	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	#VALUE!	NA	NA
Prof	PROC8a	8a -Transfer of chemicals from/to vessels/ large containers at non dedicated facilities	2.08E+02	2.08E+02	5.83E-01	5.83E-01	8.33E+02	2.33E+00	4.17E+03	1.17E+01	1.37E+01	2.74E-01

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Prof	PROC8b	8b -Transfer of chemicals from/to vessels/ large containers at dedicated facilities	4.17E+01	8.33E+01	5.83E-02	1.17E-01	4.17E+02	5.83E-01	2.08E+03	2.92E+00	1.37E+01	2.74E-01
Prof	PROC8b	8b -Transfer of chemicals from/to vessels/ large containers at dedicated facilities **at elevated temperature**	4.17E+02	4.17E+02	5.83E-01	5.83E-01	2.08E+03	2.92E+00	2.08E+03	2.92E+00	1.37E+01	2.74E-01
Prof	PROC9	9 -Transfer of chemicals into small containers (dedicated filling line)	8.33E+01	8.33E+01	2.33E-01	2.33E-01	8.33E+02	2.33E+00	2.08E+03	5.83E+00	6.86E+00	1.37E-01
Prof	PROC10	10 - Roller application or brushing	2.08E+02	2.08E+02	5.83E-01	5.83E-01	8.33E+02	2.33E+00	4.17E+03	1.17E+01	2.74E+01	5.49E-01
Prof	PROC11	11 - Non industrial spraying	8.25E+02	8.33E+02	2.31E+00	2.33E+00	4.17E+03	1.17E+01	8.33E+03	2.33E+01	1.07E+02	4.29E-01
Prof	PROC12	12 - Use of blow agents for foam production	8.33E+01	8.33E+01	2.33E-01	2.33E-01	8.33E+02	2.33E+00	4.17E+03	1.17E+01	3.40E-01	6.80E-03
Prof	PROC13	13 -Treatment of articles by dipping and pouring	8.33E+01	8.33E+01	2.33E-01	2.33E-01	8.33E+02	2.33E+00	2.08E+03	5.83E+00	1.37E+01	2.74E-01
Prof	PROC14	14 - Production of preparations or articles by tabletting, compression, extrusion, pelletisation	8.33E+01	8.33E+01	2.33E-01	2.33E-01	8.33E+02	2.33E+00	4.17E+03	1.17E+01	3.43E+00	6.86E-02

Life cycle stage	Process category code	Contributing activity	ECETOC TRA v.3.0 worker tool									
			Inhalation exposure, mg/m3								Dermal exposure, mg/kg/day	
			Low Fugacity (0.01Pa-0.5kPa)				Medium Fugacity (0.5-10kPa)		High Fugacity (>10kPa)			
			Maximum predicted exposure (SVC* cap on)	Maximum predicted exposure (SVC cap off)	Minimum predicted exposure (SVC cap on)	Minimum predicted exposure (SVC cap off)	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure	Maximum predicted exposure	Minimum predicted exposure
			Default	Default	Default with exposure modifiers **	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers	Default	Default with exposure modifiers
Prof	PROC15	15 - Use of laboratory reagents in small scale laboratories	3.33E+01	4.17E+01	9.33E-02	1.17E-01	8.33E+01	2.33E-01	4.17E+02	1.17E+00	3.40E-01	6.80E-03
Prof	PROC16	16 - Using material as fuel sources, limited exposure to unburned product to be expected	8.33E+00	8.33E+00	2.33E-02	2.33E-02	8.33E+01	2.33E-01	4.17E+02	1.17E+00	3.40E-01	6.80E-03
Prof	PROC17	17 - Lubrication at high energy conditions and in partly open process	4.17E+02	4.17E+02	1.17E+00	1.17E+00	1.67E+03	4.67E+00	4.17E+03	1.17E+01	2.74E+01	5.49E-02
Prof	PROC17	17 - Lubrication at high energy conditions and in partly open process **at elevated temperature**	1.67E+03	1.67E+03	4.67E+00	4.67E+00	4.17E+03	1.17E+01	4.17E+03	1.17E+01	2.74E+01	5.49E-02
Prof	PROC18	18 - Greasing at high energy conditions	4.17E+02	4.17E+02	1.17E+00	1.17E+00	1.67E+03	4.67E+00	4.17E+03	1.17E+01	1.37E+01	2.74E-02
Prof	PROC19***	19 - Hand-mixing with intimate contact (only PPE available)	2.08E+02	1.25E+02	2.92E+00	1.75E+00	8.33E+02	1.17E+01	4.17E+03	5.83E+01	1.41E+02	2.83E+00
Prof	PROC20	20 - Heat and pressure transfer fluids (closed systems) in dispersive use	4.17E+01	4.17E+01	1.17E-01	1.17E-01	1.67E+02	4.67E-01	4.17E+02	1.17E+00	1.71E+00	3.42E-02

* SVC – saturated vapor concentration

** – The final exposure modifiers applied to the default TRA worker exposure (ECETOC, 2012) were derived as products of (the lowest reasonable) reduction efficiency factors on a per PROC per exposure route basis. The summary of individual exposure reduction efficiency factors assumed in this analysis is provided in the table below. **Please note that concentration modifiers were not factored in.**

RMMs exposure reduction efficiencies assumed			
RMM	**Industrial**	**Professional**	**Note**
LEV	differs per PROC		inh & derm (for PROCs 7, 11, 17, 18 only)
Ventilation	0.7	0.3	inh exposure only
RPE	0.05	0.1	inh exposure only
Duration (15 min-1 hour)	0.2	0.2	inh & derm
Gloves with basic/specific training	0.05	0.1	dermal exposure only

*** - PROC 19 excludes LEV-type exposure modifier in calculations of inhalation exposure.

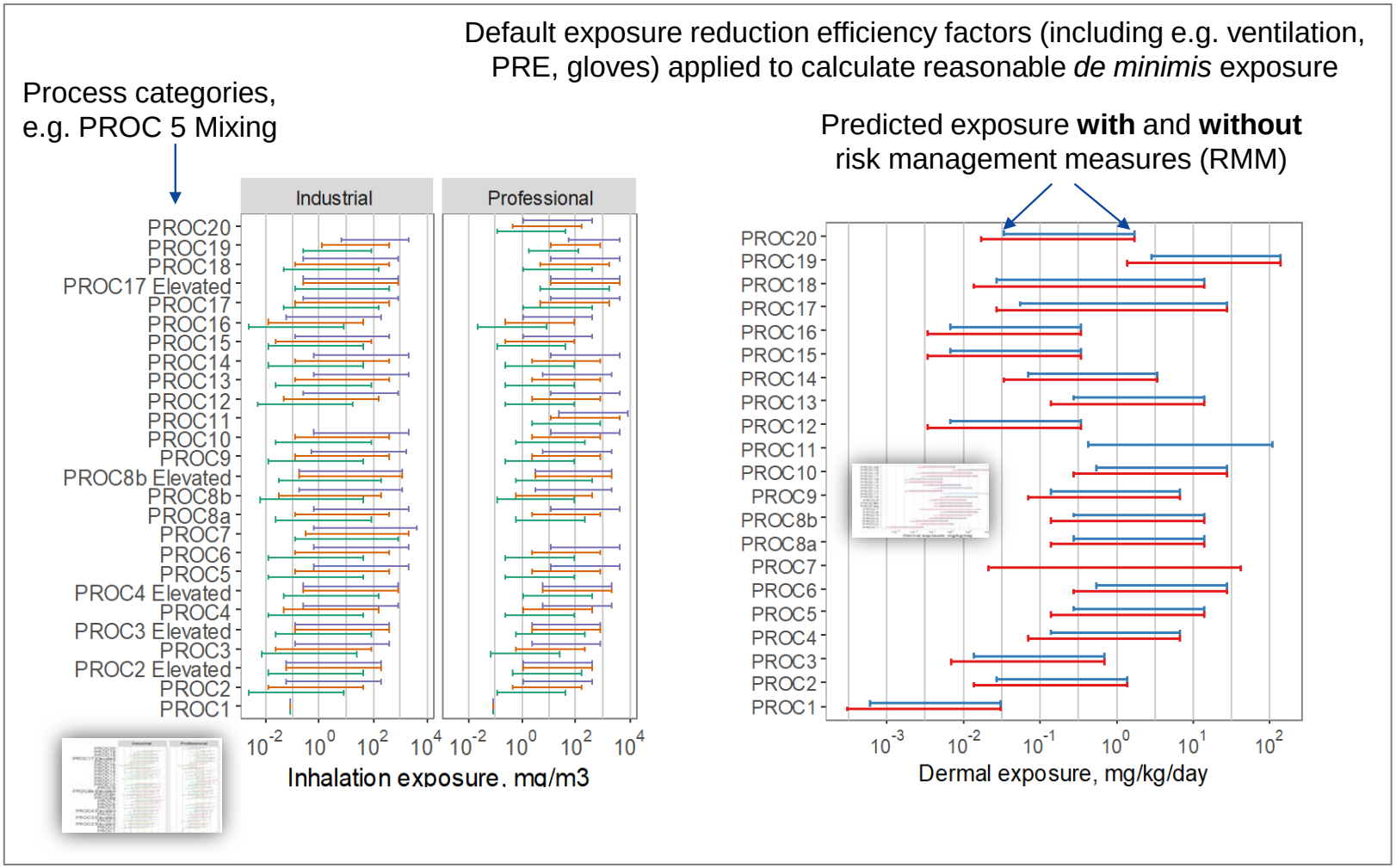

Figure II-1. Tier 1 REACH worker inhalation (left panel) and dermal (right panel) exposure calculated with ECETOC TRA v3.0 for different tasks/PROCs under various occupational settings (industrial vs. professional). Lines represent ranges of predicted exposure for a hypothetical liquid substances (MW=200g/mole) in a pure form..

Table II-2. Tier 1 REACH Consumer exposure assessment results for a pure liquid substance with VP=10 Pa and MW=200 g/mole.

Product (PC) and article (AC) categories	**ECETOC TRA v.3.1**			**ECETOC TRA v.3.1 + SCEDs**			**ESIG EGRET v.2.0**		
	inh daily	**derm daily**	**oral daily**	**inh daily**	**derm daily**	**oral daily**	**inh daily**	**derm daily**	**oral daily**
	mg/m3	**mg/kg/day**	**mg/kg/day**	**mg/m3**	**mg/kg/day**	**mg/kg/day**	**mg/m3**	**mg/kg/day**	**mg/kg/day**
PC1: Glues, hobby use	4.0E+01	1.8E+00	n/a	2.6E+01	7.5E-02		8.5E+00	1.8E+00	n/a
PC1: Glues DIY-use (carpet glue, tile glue, wood parquet glue)	8.1E+02	4.3E+01	n/a	5.4E+02	2.1E+00		2.0E+02	5.5E+00	n/a
PC1: Glue from spray	1.1E+03	1.8E+00	n/a	3.8E+02	1.8E-01		8.1E+01	1.8E+00	n/a
PC1: Sealants	8.1E+02	1.8E+00	n/a	2.7E+02	7.5E-02		3.4E+01	1.8E+00	n/a
PC3: Air care, instant action (aerosol sprays)	8.7E+02	0.0E+00	n/a	9.7E+01	0.0E+00		9.7E-02	n/a	n/a
PC3: Air care, continuous action (solid and liquid)	4.3E+01	6.0E-02	n/a	1.4E+00	2.5E-02		1.7E-01	6.0E-02	n/a
PC4: Washing car window							1.0E-04	n/a	n/a
PC4: Pouring into radiator							1.8E+00	7.1E+00	n/a
PC4: Lock de-icer							5.1E-01	1.8E+01	n/a
PC8: Laundry and dish washing products							6.7E-01	7.1E-02	n/a
PC8: Cleaners, liquids (all purpose cleaners, sanitary products, floor cleaners, glass cleaners, carpet cleaners, metal cleaners)							8.4E-01	7.1E+00	n/a
PC8: Cleaners, trigger sprays (all purpose cleaners, sanitary products, glass cleaners)							1.8E+00	1.1E+01	n/a
PC9a: Waterborne latex wall paint	8.1E+02	3.6E+01	n/a	5.4E+02	3.6E+01		7.4E+01	1.1E+00	n/a
PC9a: Solvent rich, high solid, water borne paint	8.1E+02	3.6E+01	n/a	5.4E+02	3.6E+01		7.4E+01	2.0E+01	n/a
PC9a: Aerosol spray can	6.3E+03	0.0E+00	n/a	2.1E+03	3.6E+01		1.1E+01	n/a	n/a
PC9a: Removers (paint-, glue-, wall paper-, sealant-remover)	8.1E+02	1.3E+02	n/a	5.4E+02	6.4E+01		6.7E+01	7.1E+01	n/a
PC9b: Fillers and putty	8.1E+02	6.0E+00	n/a	5.4E+02	6.4E+01		5.4E+00	1.2E-01	n/a
PC9b: Plasters and floor equalizers	8.1E+02	1.4E+02	n/a	4.0E+02	6.4E+01		6.7E+01	2.9E+00	n/a
PC9b: Modelling clay	0.0E+00	2.5E+01	1.0E+01	0.0E+00	2.5E+01	1.0E+01	n/a	2.5E+00	1.0E+00
PC9c: Finger paints	n/a	1.3E+02	6.8E+01	0.0E+00	1.3E+02	6.8E+01	n/a	1.3E+02	6.8E+01
PC12: Lawn and garden preparations	n/a	7.1E+01	1.5E+01	0.0E+00	7.1E+01	1.5E+01	n/a	7.1E+01	1.5E+01
PC13: Liquid - subcategories added: Automotive Refuelling	8.1E+02	7.1E+01	n/a	1.7E+02	1.8E-01		1.5E+00	3.5E+01	n/a
PC13: Liquid - subcategories added: Scooter Refuelling	8.1E+02	7.1E+01	n/a	1.6E+02	3.5E-01		9.9E-01	3.5E+01	n/a
PC13: Liquid - subcategories added: Garden Equipment - Use	8.1E+02	7.1E+01	n/a	5.4E+02	7.1E+01		2.5E+00	n/a	n/a
PC13: Liquid (subcategories added): Garden Equipment - Refueling	8.1E+02	7.1E+01	n/a	1.4E+02	3.5E-02		8.1E-01	7.0E+01	n/a
PC13: Liquid (subcategories added): Home space heater fuel	8.1E+02	7.1E+01	n/a	1.8E+02	3.5E-02		2.3E-01	3.5E+01	n/a

Product (PC) and article (AC) categories	ECETOC TRA v.3.1			ECETOC TRA v.3.1 + SCEDs			ESIG EGRET v.2.0		
	inh daily	derm daily	oral daily	inh daily	derm daily	oral daily	inh daily	derm daily	oral daily
	mg/m3	mg/kg/day	mg/kg/day	mg/m3	mg/kg/day	mg/kg/day	mg/m3	mg/kg/day	mg/kg/day
PC13: Liquid - subcategories added: Lamp oil	8.1E+02	7.1E+01	n/a	1.4E+02	1.8E-01		1.3E-01	3.5E+01	n/a
PC15: Waterborne latex wall paint							7.4E+01	1.1E+00	n/a
PC15: Solvent rich, high solid, water borne paint							7.4E+01	2.0E+01	n/a
PC15: Aerosol spray can							1.1E+01	n/a	n/a
PC15: Removers (paint-, glue-, wall paper-, sealant-remover)							6.7E+01	7.1E+01	n/a
PC16: Heat tranfer Liquids							4.0E+00	7.8E+01	n/a
PC17: Hydraulic fluids Liquids							4.0E+00	7.8E+01	n/a
PC18: Inks and toners.							1.0E+01	1.2E+00	n/a
PC23: Leather Polishes, wax / cream (floor, furniture, shoes)							4.1E+01	3.6E+01	n/a
PC23: Leather Polishes, spray (furniture, shoes)							1.1E+01	3.6E+01	n/a
PC24: Lubricants Liquids	8.1E+02	7.1E+01	n/a	4.5E+01	7.1E-02		4.0E+00	7.8E+01	n/a
PC24: Lubricants Pastes	0.0E+00	2.9E+01	n/a	0.0E+00	2.9E+01		n/a	1.6E+01	n/a
PC24: Lubricants Sprays	2.2E+03	3.6E+01	n/a	1.5E+03	3.6E+01		5.7E+00	3.6E+01	n/a
PC27: Plant protection							n/a	7.1E+01	1.5E+01
PC31: Polishes, wax / cream (floor, furniture, shoes)	8.1E+02	7.1E+01	n/a	5.4E+02	3.6E+01		4.1E+01	3.6E+01	n/a
PC31: Polishes, spray (furniture, shoes)	9.9E+02	7.1E+01	n/a	7.0E+02	3.6E+01		1.1E+01	3.6E+01	n/a
PC34: Textile dyes							1.8E+01	1.4E-01	n/a
PC35: Cleaning (Hand) Dish washing products	8.1E+02	8.6E+01	n/a		8.6E+01		6.7E-01	7.1E-02	n/a
PC35: Cleaning Laundry products	8.1E+02	8.6E+01	n/a	1.8E+02	4.3E+01		6.7E-01	7.1E-02	n/a
PC35: Cleaners, liquids (all purpose cleaners, sanitary products, floor cleaners, glass cleaners, carpet cleaners, metal cleaners)	8.1E+02	7.1E+01	n/a	1.6E+02	1.4E+01		8.4E-01	7.1E+00	n/a
PC35: Cleaners, trigger sprays (all purpose cleaners, sanitary products, glass cleaners)	1.0E+02	2.9E+01	n/a	3.0E+01	1.4E+01		1.8E+00	1.1E+01	n/a
PC36: Water softeners							n/a	1.3E-03	3.0E-04
PC37: Water treatment							n/a	1.3E-02	3.1E-03
PC38: Welding and soldering							3.8E+00	n/a	n/a

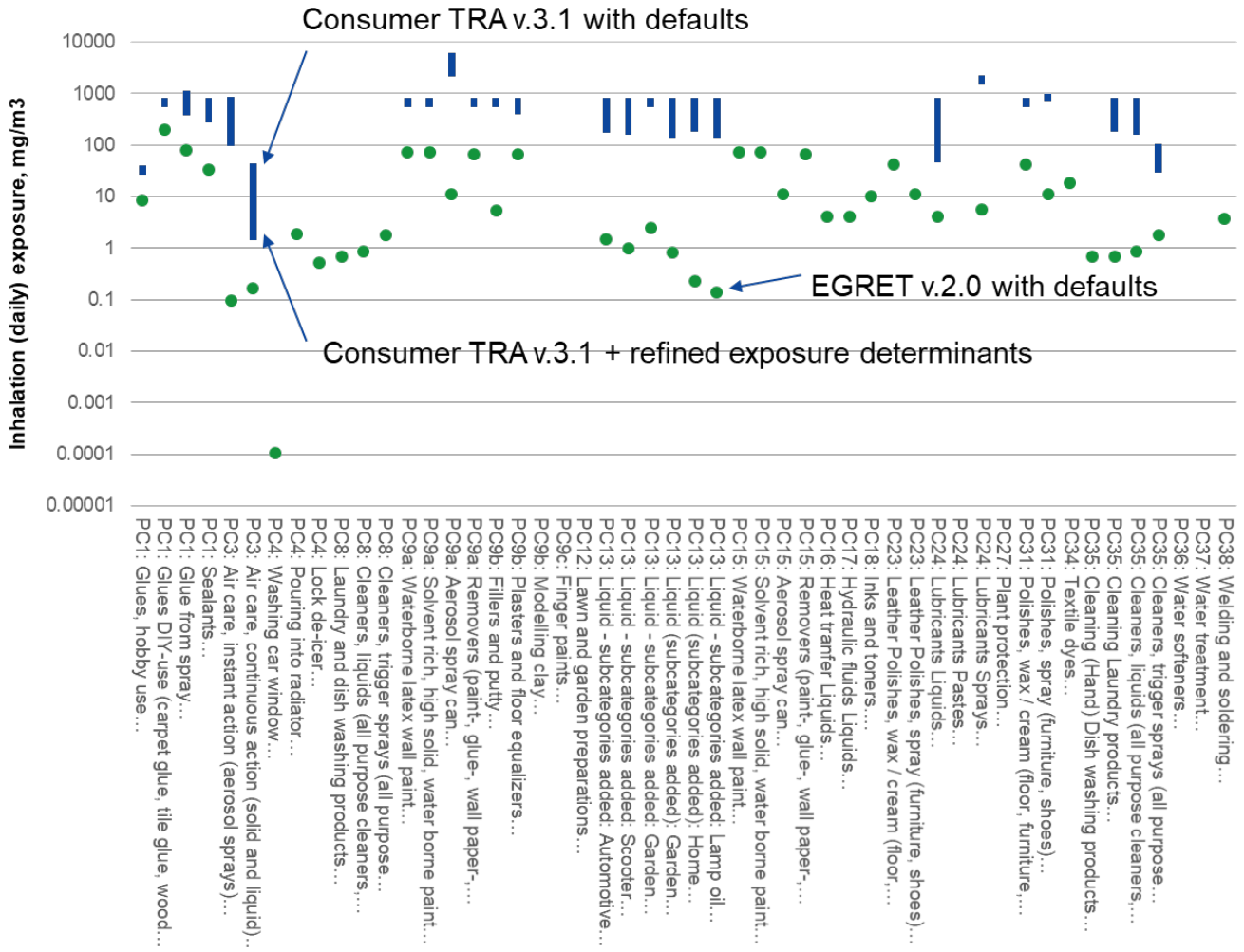

Figure II-2. Tier 1 REACH consumer inhalation daily exposure predictions for a pure liquid substance with VP=10 Pa and MW=200 g/mole. Upper ends of blue bars represent default exposure predicted with ECETOC TRA v.3.1, lower ends of blue bars represent TRA v.3.1 predictions redined with SCEDs inputs. Green dots represent EGRET v.2.0 daily exposure estimates.

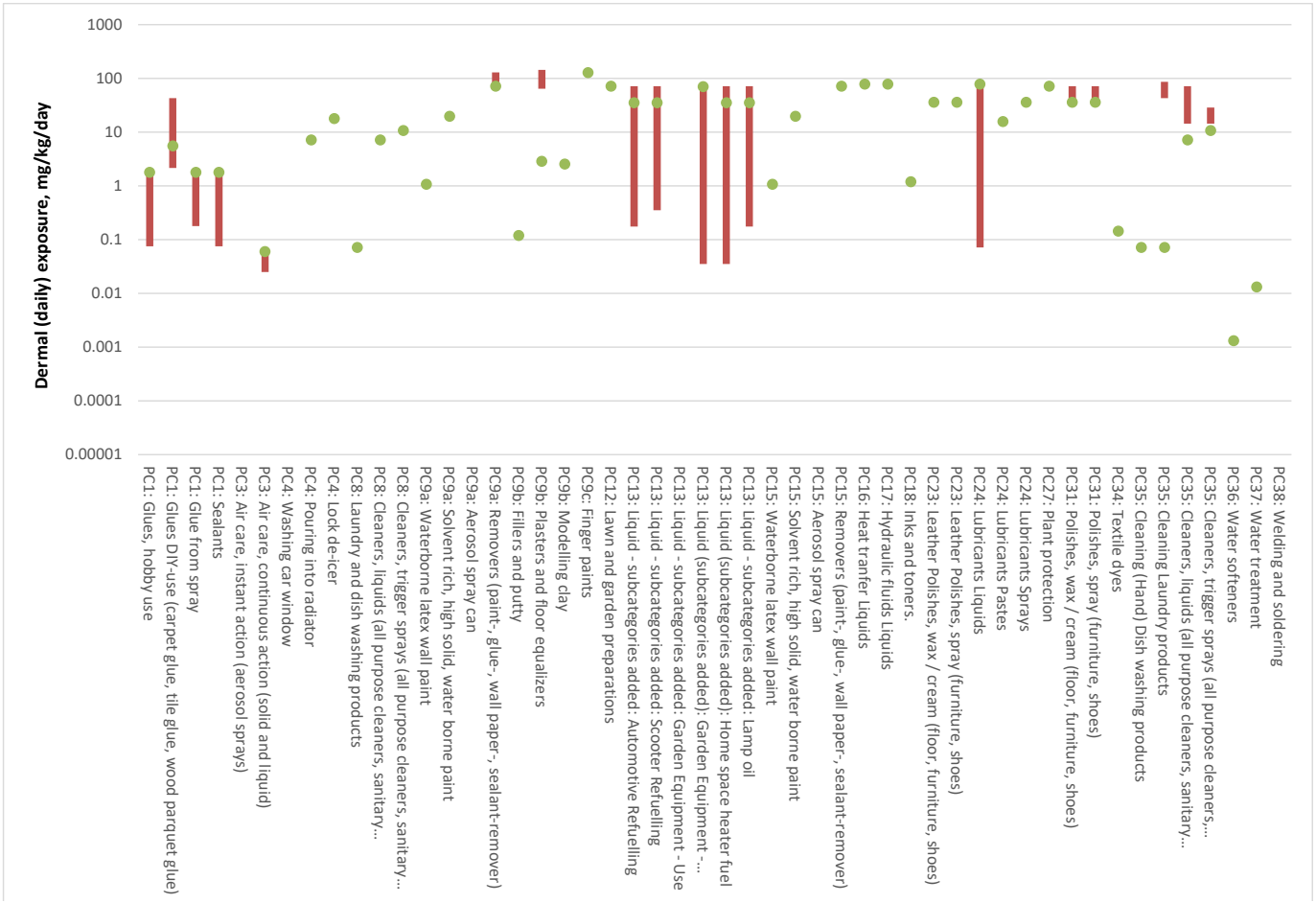

Figure II-3. Tier 1 REACH consumer dermal daily exposure predictions for a pure liquid substance of MW=200 g/mole. Upper ends of red bars represent default exposure predicted with ECETOC TRA v.3.1, lower ends of red bars represent TRA v.3.1 predictions refined with SCEDs inputs. Green dots represent EGRET v.2.0 daily exposure estimates

Higher tier REACH exposure assessment for EBA.

In contrast to Tier 1 screening exposure models, higher tier tools usually require more detailed knowledge on the exposure scenario in order to reliably estimate worker or consumer exposure. The expectation (by ECHA) is that the assessor provides supporting data for any exposure refinement parameter employed in the assessment. In the absence of supporting data, a worst-case approach should be followed for EBA-type of exposure assessment integrating minimal or very basic exposure controls.

For workers, due to prohibitively large number of theoretical combinations of input parameter in the reviewed higher tier worker exposure models (e.g. up to 2×10^9 in ART), the analysis of theoretically possible exposure ranges per PROC was not feasible. Instead, the findings of Riedmann et al., 2015, who conducted the local one-at-a-time sensitivity analysis of ECETOC TRA v.3, Stoffenmanager v.4.5, and ART 1.5, can be leveraged to inform worker exposure assessments for EBA.

The study by Riedmann et al.,2015 provides detailed evaluation of the robustness of the models and identifies the dominant factors contributing to decision making uncertainties. These include the relative influence of NF – near field, FF – far field, t – exposure duration, Seg – segregation, Sep – separation, D – dispersion, a – background, LC – local controls, H – handling/activity emission, E – intrinsic emission scores. Figures II-4 A and B (adapted from Riedmann et al., 2015) illustrate the ranges of calibrated exposure estimates for various forms of a substance (i.e. vapors, mists, and dusts) in Stoffenmanager v.4.5 and ART 1.5, respectively. They provide a general idea of the lower bounds of inhalation worker exposure that can be predicted using these higher tier models.

For Stoffenmanager, the unitless exposure score covers 16, 15, and 11 orders of magnitude for vapors, mists and dusts, respectively. The ranges of the 50th and 95th percentile exposure estimates cover six to eight orders of magnitude and ten to eleven orders of magnitude (10^{-7}–10^4 mg/m3; Figure II-4 A), respectively.

For ART the spread is much wider: the respective exposure estimates in mg/m3 (50th percentile) cover 26, 22, and 26 orders of magnitude for vapors, mists, and dusts, respectively (Figure II-4 B). The most important factors are the local control LC (26–34%) and the source emission E (17–32%). Dilution is slightly more important for far-field scenarios than for near-field scenarios. The least important factors, apart from the background, are the segregation and the separation (3–4%). The lower range of exposure estimates for vapors in ART is $<10^{-16}$ mg/m3. The relevance of concentrations in the ppb range and lower is questionable, however, as they tend to fall below limits of detection for monitoring methods. Interestingly, Figure II-4 B provides that in ART using only the intrinsic emission factor alone, i.e. the basic determinant of worker scenario/activity, can bring the exposure estimate to inhalation TCC level for very hazardous chemicals (Cramer class III). Inclusion of other factors/determinants (e.g. local controls) will bring the exposure even lower.

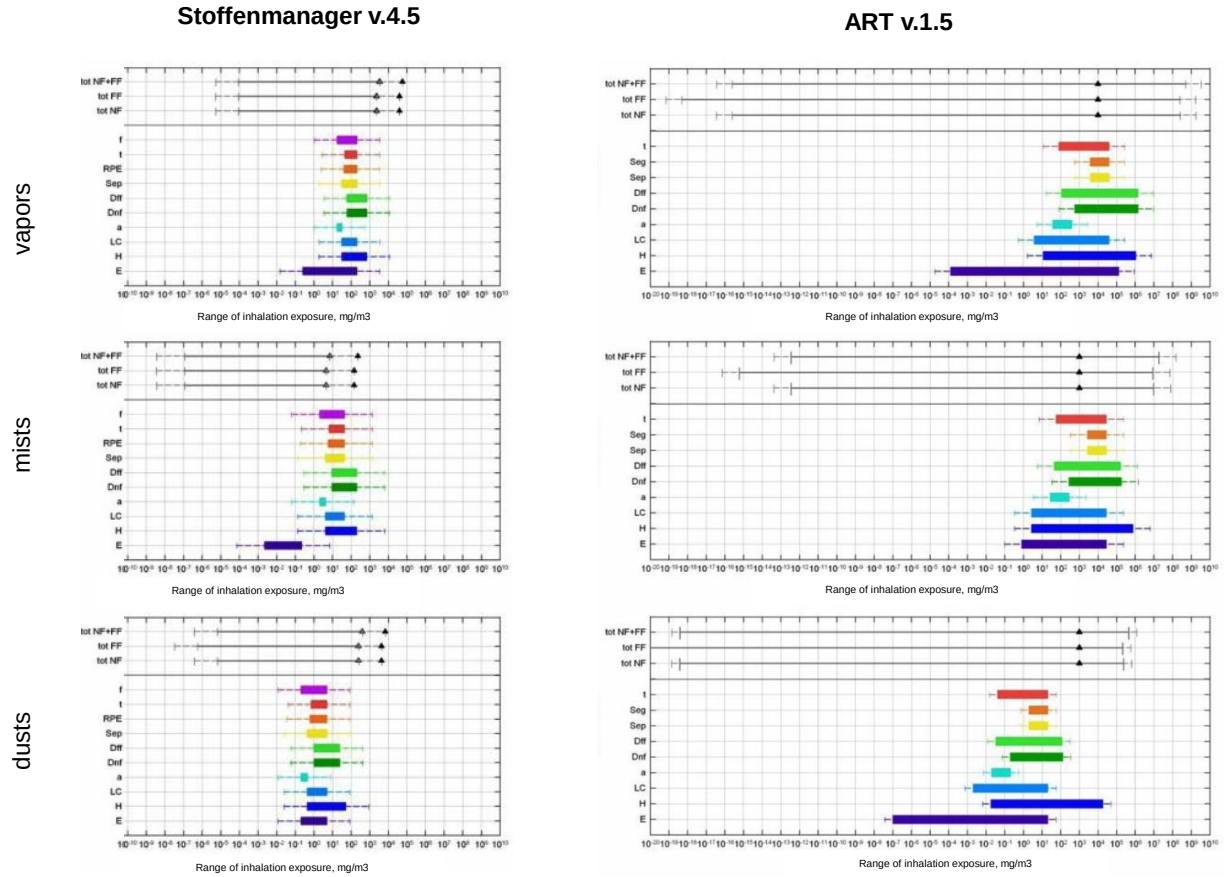

Figure II-4. Ranges of calibrated inhalation worker exposure predicted with higher tier REACH tools Stoffenmanager 4.5 and ART v.1.5. The grey solid lines in the upper part of the graphs give the P50 and dashed lines give the P95 confidence intervals for P50 (Δ; for Stoffenmanager only) and P95 (▲) of exposure. The ranges of exposure estimates for single determinants (assumes all other factors are equal to zero) are given in the colour bars (50th percentile) and dashed lines (95th percentile).

Table II-3 below captures the relative importance of compartments (in percentage), constituting different modifying factors, to the initial exposure estimate for the three evaluated worker exposure models. The source compartment comprises ~50–75% of the total exposure range for the three models and therefore has the largest influence. The dilution factor contributes approximately two times as much in ART as it does in ECETOC TRA v.3 (8%). Notably, Stoffenmanager appears to be the most balanced with regards to physical phenomena such as source emission and dilution. These data is deemed useful for the evaluation of exposure refinement potential based on limited contextual information.

The authors conclude that in Stoffenmanager the decision-making uncertainties in a modifying factor are less severe compared to other tools. The choice of the adequate model should ultimately be determined by the quality of the available exposure data: when the entry data are uncertain concerning two or more decisions in the entry parameters, the assessors should consider using Stoffenmanager; ART may lead to more accurate results in well-documented exposure situations.

Table II-2. Relative importance of compartments (in percentage) to the exposure estimate for the ECETOC TRA v3, Stoffenmanager 4.5, and ART 1.5 Models.

Exposure Model	Source	Dilution	Time	*RPE*
ECETOC v.3	59	8	14	19
Stoffenmanager v.4.5	45	21	24	10
ART v.1.5	74	16	10	0

With regards to higher tier dermal exposure assessments, to date the Riskofderm model is thought to be the most reasonable tool for predicting dermal exposure to substances with VP<500 Pa in industrial and professional settings. The validity and adequacy of the model is relatively well-known for situations resembling those measured in the data set underpinning the model, some of which may be relevant for the scenarios assessed under REACH.

The development of dermal Advanced REACH Tool (dART) is ongoing (Goede et al., 2019; McNally et al., 2019). The beta-version of dART is capable of predicting hand exposure to low volatile liquids (VP ≤ 10 Pa at 20°C), including solids-in-liquid products, based on the three key processes involved in dermal mass transport, i.e. deposition, direct emission and contact, and transfer. It is noteworthy, however, that to date dART has overall a poorer precision than the (inhalation) ART for dusts and vapors. Hence, reliability of its predictions will depend largely on the competence of a user and the quality of contextual information available for an exposure scenario of question.

For consumers, ConsExpo is considered to be the main REACH exposure models that enables higher tier exposure estimations and includes a product database with default exposure determinant inputs. Several studies (e.g. ECETOC, 2012; R et al., 2015; Feld-Cook et al., 2019; Delmaar and Meesters, 2020) indicate that, in general, for evaluated scenarios ConsExpo provides lower (i.e. more refined) consumer exposure estimates that Tier 1 REACH models for both inhalation and dermal routes, approaching measured exposure levels. The difference between lower and higher tier REACH consumer exposure predictions can span several orders of magnitude, depending on which input values and calculation algorithms are selected for estimating exposure.

Before moving to higher tier ConsExpo exposure modelling, however, the assessor should consider first the possibility to refine Tier 1 estimates using the information on infrequent use of a product (where SCEDs data indicate infrequent use). One can choose to follow either the frequency banding approach in ECETOC TRA v.3.1 or derive a special infrequent DNEL for consumers following ECHA's R.15 guidance (ECHA, 2016b).

Overall, for the EBA-oriented exposure assessments it is critical that the predicted low exposures are not underestimated. The registrant can help reduce uncertainty by comparing the estimates from a range of sources, including different tools and measured data. Given the uncertainty inherent in many tools, generation of RCRs close to 1 may indicate that further investigation is necessary, such as further iteration within the tool or assessment by other means. Use of single tool estimates is unlikely to be persuasive enough for the purposes of assessing circumstances related to strictly controlled conditions or for proving the low level exposures that may be demanded by REACH authorisation or when justifying EBA.

Acronyms

ADME	Absorption, Distribution, Metabolism, and Excretion
APV	Annual Production Volume
AUC	Area Under the Curve
COSHH	Control of Substances Hazardous to Health
CSA	Chemical Safety Assessment
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
EBA	Exposure Based Adaptations
EC	European Commission
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EOGRTS	Extended One-Generation Reproductive Toxicity Study
ERC	Environmental Release Categories
EU	European Union
FCM	Food Contact Material
FOB	Functional Observational Battery
GPMT	Guinea Pig Maximisation Test
LC50	Lethal Concentration with 50% mortality
LD50	Lethal Dose with 50% mortality
LLNA	Local Lymph Node Assay
LOD	Limit of Detection
MMAD	Median Mass Aerodynamic Diameter
NOAEL	No Observed Adverse Effect Level
OC	Operational Conditions
OECD	Organisation for Economic Co-operation and Development
PC	Product Category
PPE	Personal Protection Equipment
PROC	Process Categories
QSAR	(Quantitative) Structure Activity Relationship
RCR	Risk Characterization Ration

REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RISK21	Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century Project
RMM	Risk Management Measures
SCC	Strictly Controlled Conditions
SCCS	Scientific Committee on Consumer Safety
SCEDs	Specific Consumer Exposure Determinants
SWED	Specific Worker Exposure Determinants
TEM	Transmission Electron Microscopy
TK	Toxicokinetics
TR	Technical Report
TRA	Targeted Risk Assessment
TTC	Threshold of Toxicological Concern

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