Assessment Factors to Derive DNELs – Critical Evaluation of the Status Quo

Technical Report No. 136

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

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Technical Report No. 136

Brussels, June 2020

ISSN-2079-1526-136 (online)

ECETOC Technical Report No. 136

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Assessment Factors to Derive DNELs

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SUMMARY

Establishment of the Derived No-Effect Level (DNEL) is a key step in safety assessments of chemicals under the European Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (EU, 2006). European Chemicals Agency (ECHA) guidance has defined the process for derivation of DNELs based upon recognised international practices and the need for extrapolation from experimental data (most likely determined in animals) to the human exposure situation by the application of assessment factors (AFs). While ideally AFs would be developed based on substance-specific information i.e. Chemical Specific AFs (CSAF) in practice scarcity of appropriate data necessitates the use of 'default' AFs.

AFs are used to address the differences between laboratory data and humans, taking into account of interspecies differences, human variability including sensitive sub-groups as well as differences in study duration compared with worker and consumer exposure. The approach of combining an AF of 10 for intraspecies variability and 10 for interspecies variability to form an overall default AF of 100 has become embedded in regulatory practices throughout the world and can be regarded as a matter of science policy.

ECETOC has reviewed the science on AFs three times over that past 25 years (TR 68; ECETOC, 1995; TR 86; ECETOC, 2003 and TR 110; ECETOC, 2010) and concluded that the default approach is conservative and that the available science, albeit limited, supports the use of alternative (lower) factors in some cases. This current review was initiated to establish if the available science has changed over the past 10 years and to summarise industry's experience in applying the alternative ("informed") AFs proposed by ECETOC in 2010.

In the case of AFs for intra- and inter-species variation, the current review failed to reveal significant new scientific data beyond that which was available in 2010. The underlying data still supports the views expressed in the earlier ECETOC reviews; however, it has become clear that with regard to some details, there are divergences between ECHA's and ECETOC's interpretation of the statistical aspects of the data, and how to combine them into appropriate deterministic assessment factors. At this interface of risk assessment and risk management, any future change in regulatory policy and practice will require further advancements in the characterisation of variability and uncertainty. It is recommended that the ECETOC alternative AFs as recommended in TR 110 (ECETOC, 2010) are only used for REACH submissions if supported by chemical-specific justification, including transparent documentation.

In the case of the AFs for study duration, it is recognised that in recent years large quantities of mammalian toxicity test data has been generated under the REACH compliance program. Recent analysis of this and other data points to the need to critically review the AFs and associated guidance to account for study duration to avoid divergent viewpoints and practices developing.

Bhat et al., 2017 reviewed a number of cases where CSAF were applied in a regulatory context, and provide recommendations on how to document the underlying evidence. While the high cost of developing CSAF limits the approach to a relatively small number of high profile/value chemicals, these CSAF case studies support the viewpoint that default AFs are in some cases overly conservative. There may be an opportunity to use Read-Across approaches to apply this learning to the benefit of other chemicals, as discussed on the basis of a case study in this report.

1. INTRODUCTION

In the context of the European Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (EU, 2006), the European Chemicals Agency (ECHA) has defined the terms Derived No-Effect Level (DNEL) and Derived Minimal-Effect Level (DMEL) as "*the level of chemical exposure above which humans should not be exposed*" and made available technical guidance on how they should be derived and used in Chemical Safety Assessments.

A key step in the calculation of a DNEL is the extrapolation from the experimental data (most likely determined in animals) to the human exposure situation. This is achieved by applying assessment factors (AFs) to account for variability and uncertainty.

The R8 guidance (ECHA, 2012) in section (4.3 c) describes that ideally the AFs would be developed based on substance-specific information i.e. chemical specific AFs (CSAF), but that in practice scarcity of appropriate data necessitates the use of 'default' AFs.

These 'default' AFs were proposed in 1954 based upon limited data in animals and humans and despite only being the subject of minimal refinement in subsequent years have used widely by governmental authorities and international agencies across the world, especially for product-related regulation, while occupational safety limits often were derived with other methodology. These 'default' AFs are generally recognised as conservative estimates and their use was contested by ECETOC in their review on AFs in 1995 (TR 68; ECETOC, 1995) and again in 2003 (TR 86; ECETOC, 2003) and 2010 (TR 110; ECETOC, 2010) as not being adequately justified and introduced the term 'informed' to describe AFs that they believed were more appropriate.

Some registrants under REACH relied on these ECETOC 'informed' AFs only to find that they were rejected by ECHA as they were not considered sufficiently justified.

Guidance exists for developing Chemical Specific Adjustment Factors (CSAF) (e.g. WHO IPCS, 2005) but to date few examples exist (Bhat et al., 2017). Within ECETOC, several companies have formed a Task Force aimed at determining if the state of knowledge surrounding AFs had advanced since the last ECETOC review almost a decade ago and to identify opportunities for both refinement of default AFs and broader use of CSAFs.

2. GENERAL CONSIDERATIONS

2.1 DNEL versus OEL

For some chemicals there exist health-based occupational or workplace exposure limits (OEL) set by EU National Competent Authorities, EU indicative occupational exposure limit value (IOELV) set by DG Employment's Scientific Committee on Occupational Exposure Limits (SCOEL), or workplace exposure limits/standards (OEL/OES) set by companies in the absence of an official limit value being set. REACH Guidance on Information Requirements and Chemical Safety Assessment GD (ECHA, 2012), Appendix R.8-13 describes that existing occupational exposure limits and/or the underlying information used for setting them can be used to derive DNEL values under certain circumstances. The guidance document (GD) describes three situations:

- Where an EU indicative occupational exposure limit value (IOELV) has been set, this may be taken as a $DNEL_{worker}$. This requires that the exposure route and duration for the DNEL is the same as that for the IOELV and no new scientific information is available that would lead to a different value being set.
- Where an EU binding occupational exposure limit value (BOELV) has been set by taking into account socio-economic factors and technical feasibility, this cannot be used in place of a DNEL. However, the toxicological evaluation of the health effects described in the assessment may be used and taken into account for setting a DNEL.
- Where a health-based national OEL has been set, the toxicological information used must be evaluated and any differences to the REACH GD DNEL calculation method must be taken into account.

Under any of these conditions, it would not be necessary to use the REACH GD approach and AF for defining $DNEL_{worker}$ While ECHA guidance does not refer to workplace exposure limits/standards (OEL/OES) set by companies it is reasonable to conclude that DNELs derived according to the REACH GD would take precedence.

Some registrations under REACH used this option to avoid having to derive a DNEL and achieve consistency with existing work practices and control measures. However, divergent standards proposed by ECHA's risk assessment committee (RAC) and SCOEL for N-methyl-2-pyrrolidone (NMP) led the European Commission to ask the two agencies to create a joint taskforce to compare their methodologies. The resulting report highlighted significant differences between the methodologies used by SCOEL and in ECHA guidance that RAC applies to derive exposure standards including the preference for SCOEL to weight good quality human data compared with RAC to prefer animal data as a starting point, with applied assessment factors (ECHA, 2017a). Thus, RAC selected developmental effects in animals while SCOEL has chosen respiratory and local irritation in humans as the primary critical adverse effect. In March 2018 the Commission '*questioned the need to have at EU level two different committees dealing with the evaluation of the same chemicals*' and since 2019 ECHA and its Committee for Risk Assessment (RAC) have been supporting the European Commission's Directorate-General for Employment, Social Affairs and Inclusion (DG EMPL) by providing scientific opinions on OELs. While RAC has indicated its willingness to consider reliable human data, the fact that most chemicals will be data poor in this regard signals the likelihood that ECHA will preferentially require DNELs to be derived from animal data in the future.

2.2 DNEL versus DMEL

As explained previously in the ECETOC 2010 report, the first decision when developing a risk assessment, the risk assessor is the determination of the likely mode of action (MoA) and whether the critical effect observed (or to be assumed) is threshold-based or not. For stochastic types of processes, especially mutagenicity and genotoxic carcinogenicity, the default assumption prevailing in current regulatory schemes is that there is no threshold and the dose-response relation is based, in principle, on linear extrapolation to a dose of 'very low concern'. Under these conditions, no classical DNEL can be established and this case will not be considered further in this report. However, in the event of this paradigm changing, the concepts discussed below could be adapted/applied. If the MoA is threshold-based, the dose descriptors are converted into points of departure (POD) and then extrapolated via AF as described in Section 4 of this report.

2.3 The point of departure (POD)

2.3.1 Identification of the POD

The standard information requirements under REACH are described in Annexes VI to X of the regulation and depend on the quantity of the substance that is manufactured or imported into the EU/EEA. An initial step in the process of registration is the gathering all existing physicochemical, toxicological and ecotoxicological information that is relevant and available to the registrants (regardless of whether information on a given endpoint is required or not at the specific tonnage level). Where the available information is insufficient to satisfy the data requirements and waiving or read-across is not possible, further testing will be required. For many toxicological endpoints this typically involves vertebrate testing i.e. studies in animals. Accordingly, the REACH GD predominantly focuses on extrapolation of risk to humans from data in animals.

For some high-production volume chemicals with widespread use, there may be evidence for the absence or presence of adverse health effects in humans. This may include but is not limited to anecdotal evidence, market surveys, analytical epidemiology studies, descriptive or correlation epidemiology (morbidity and mortality) studies, case reports, clinical studies, poison centre information, occupational disease registries or other occupational surveillance systems. According to the provisions of Annex XI of the REACH Regulation "Historical Human Data" can be used to adapt the standard testing requirements of Annexes VII to X provided that the quality of the data is properly assessed and found to be adequate. Furthermore, the human health hazard assessment as defined in Annex I of REACH comprises four steps, the second of which is evaluation of human information.

REACH TDG Section R.8 provides guidance as to what ECHA expects regarding the assessment of the quality of the human data and refers the registrant to Annex XI of the REACH Regulation setting out the following general criteria for assessing the adequacy of the data for adaptation of the standard testing requirements.

These are as follows:

1) the proper selection and characterisation of the exposed and control groups;
2) adequate characterisation of exposure;
3) sufficient length of follow-up for disease occurrence;
4) valid method for observing an effect;
5) proper consideration of bias and confounding factors; and
6) a reasonable statistical reliability to justify the conclusion.

For further explanation and guidance, the reader is referred to page 149 onwards in the R8 guidance (ECHA, 2012) as well as the criteria and scoring system described in the read-across assessment framework (RAAF) (ECHA, 2017b).

As underlined in Section 4 of the R8 guidance, a weight of evidence (WoE) approach is considered essential for risk assessment based on epidemiological and other human data. In this regard, ECETOC TR 104 (ECETOC, 2009) provides a useful guide for an integrative framework for human and animal data that assesses the quality of each database with respect to a given chemical or exposure scenario. A scheme is presented to score human data quality and categorise animal data to help with the decision to base the risk assessment on information available for humans or animals or on a combination of both of them. The AF which are recommended to be used with human data are in many cases different from those used with animal data and are described in Section 8 of the TR104 report and Section 5 in the TR 110 report (ECETOC, 2010) and is not elaborated further in this report.

2.3.2 Modification of the POD

While the modification of the POD to correct the starting point to take account of differences in exposure pattern (duration, frequency, route) between animals and humans its strictest sense is not related to the choice of AF, this may have a major impact on the derived DNEL. REACH guidance (R.8.4.2 b) explains that "*In a few situations, the effects assessment is not directly comparable to the exposure assessment in terms of exposure route, units and/or dimensions*" thereby requiring 'modification' of the relevant dose descriptor(s) per endpoint to the correct starting point (i.e., correct the unit of exposure. The GD gives examples of such situations including:

1. If for a given human exposure route there is a dose descriptor for the same route in experimental animals but for that particular exposure route there is a difference in bioavailability between experimental animals and humans at the relevant level of exposure.
2. If for a given human exposure route there is not a dose descriptor for the same route (in experimental animals or humans).
3. Differences in human and experimental exposure conditions.
4. Differences in respiratory volumes between experimental animals (at rest) and humans (light activity).

This report will not address the scientific issues surrounding derivation and adjustment of POD, as this is comprehensively addressed in the REACH R8 guidance (ECHA, 2012) from page 158 onwards, other than to recognise that a DNEL should not be calculated if no hazard is observed i.e. if no adverse effects are observed at the limit dose (see also section 4.2).

3. GENERAL CONSIDERATION FOR THE SELECTION AND APPLICATION OF ASSESSMENT FACTORS

For reasons given earlier, in all but a few cases the only data available upon which to base the human health assessment that will be in animals or alternative methodologies (in vitro, silico, QSAR etc.). The derivation of DNEL from human data is described in Section 8 of the TR104 report and Section 5 in the TR 110 report and is not elaborated further in this report. The use of alternative methodologies (in vitro, in silico, QSAR etc.) is not addressed in this report so the remainder of this section, as well as Sections 4 and 5, pertain to the use of animal data.

The next step in the calculation of a DNEL after modification of the POD is to extrapolate from the experimental data (most likely determined in animals) to the human exposure situation. This is achieved by applying assessment factors (AFs) to account for variability and uncertainty.

The R8 guidance in section (4.3 c) describes that ideally the AFs would be developed based on substance-specific information i.e. chemical specific AFs, but that in practice scarcity of appropriate data necessitates the use of default AFs. The background to the development of these factors is described in the following section.

4. BACKGROUND TO THE DEVELOPMENT OF DEFAULT (AFS) AND CHEMICAL SPECIFIC ASSESSMENT FACTORS (CFAS)

For decades, the general practice used to derive "safe doses" for subsequent use in risk assessment involved incorporation of uncertainty factors (UFs) or assessment factors (AFs) to address differences between species (i.e. animal-to human extrapolation) and between humans (i.e. interindividual or intraspecies variability) and database deficiencies and/or uncertainties such as the nature of the POD i.e. LOAEL vs NOAEL, or the study duration as compared with lifetime exposure in humans (WHO/IPCS 1994).

The concept of using assessment factors to bridge between toxicological information, usually generated through studies with experimental animals, and the human situation is coded in the GD (ECHA, 2012) and key to the risk (Chemical Safety) assessment process. The GD and associated guidance refers to both 'default' assessment factors and 'substance-specific' or 'case-specific' assessment factors.

ECETOC in their reviews in 2003 (TR 86; ECETOC, 2003) and 2010 (TR 110; ECETOC, 2010) introduced the term 'informed' to describe assessment factors that they believed were more appropriate than the 'default' ones recommended in the GD and these were used in preference by some registrant only to be rejected within the review process as they were not considered sufficiently justified. With the hindsight of this experience within the REACH process and the wider experience within the international risk assessment community on the development of 'chemical specific' assessment factors or CSAF it is important to gain an understanding of how these factors have evolved, their intended application and practical limitations.

Bhat et al., in their 2017 review paper on 'Chemical-Specific Adjustment Factors' (CSAF) described the evolutionary timeline of the major developments surrounding the WHO/IPCS (2005) CSAF guidance and in so doing highlight the background to the development of 'default adjustment factors' (figure 4.1).

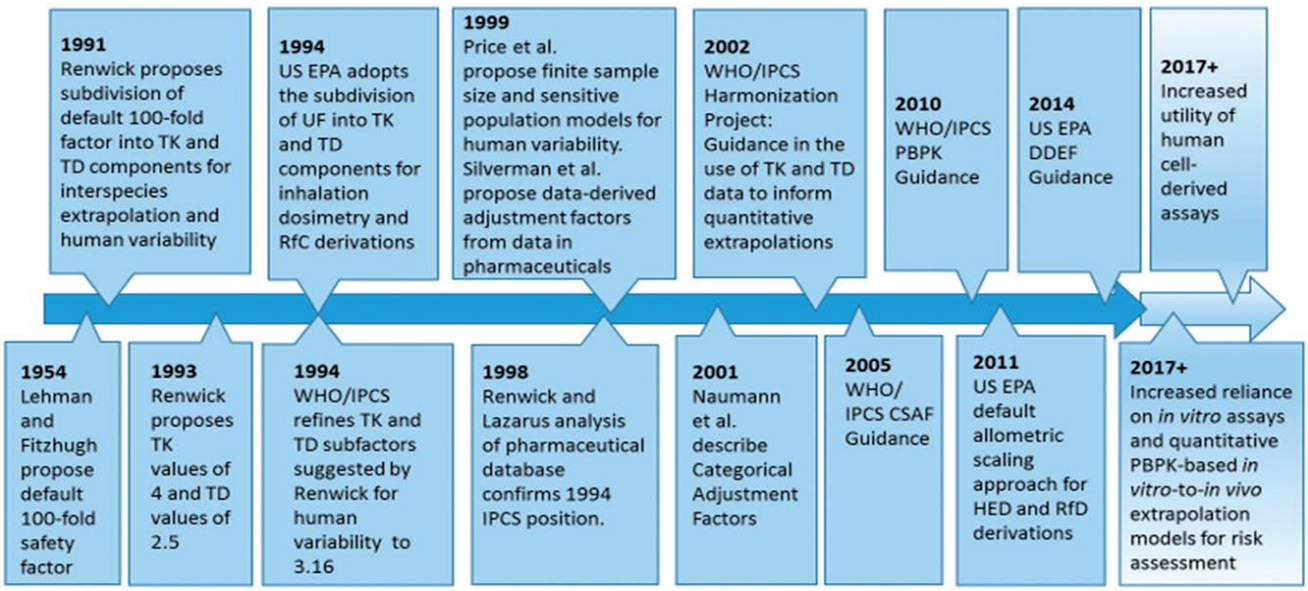

Figure 4.1 Evolutionary timeline of the major developments surrounding the WHO/IPCS (2005) CSAF Guidance.

It is immediately apparent that the overall factor of 100-fold extrapolation nowadays often referred as "default adjustment factor" finds its roots as long ago as 1954 in the publication by Lehman and Fitzhugh. The value of 100 was based on a limited analysis of the variation between and within species in the biological processes relevant to the adverse effects for a range of chemicals which had information available in both experimental animals and humans at the time.

Much later, in 1993, Renwick proposed that the default 10-fold uncertainty factors for interspecies differences and for intraspecies differences (human variability) encompass both Toxicokinetics (TK) and Toxicodynamics (TD) considerations. This publication proposed that the overall factor of 10 for interspecies differences should be comprised of a combination of a 4-fold TK subfactor and a 2.5-fold TD subfactor. The TK/TD split was based on underlying data in rats (the most commonly used test species) and humans and consistent with an approximately 4-fold difference (according to the three-quarter power of the ratio of the body weight between rats and humans). This accounts for species differences in basic physiological parameters, cardiac output, renal and liver blood flows i.e. the major determinants of clearance/elimination.

WHO/IPCS in 1994 took the concept of subdivision of the factor of 10 for intraspecies differences first proposed by Renwick and assigned the TK and TD aspects into two 3.16-fold (normally rounded to 3.2) subfactors based upon kinetic parameters and physiologically based pharmacokinetic (PBPK) and pharmacodynamic (PD) modelling for a range of toxicological or therapeutic responses to pharmaceutical agents (Renwick, 1991, 1993; Renwick & Lazarus, 1998).

In 1995 ECETOC investigated the role of assessment factors in human health risk assessment (TR 68; ECETOC, 1995) and while recognising the standing of the "traditional" 100-fold assessment factor, considered it "*unclear based upon the literature whether this was based upon analysis of data, and if so what fraction of the population it was expected to protect*".

ECETOC revisited the topic in 2003 (TR 86; ECETOC, 2003) and after reviewing the available evidence at that time reaffirmed the earlier findings and concluded that for interspecies extrapolation from animals (rats) to humans for systemic effects that "*a total default AF of 5 was sufficient to account for interspecies variability after scaling (*i.e. the TD factor*) and for any differences in intraspecies variability (*i.e. TK and TD*)"*.

The default subfactors of 10 and 10 were adopted by various national and international organisations during the 90's and 2000's (US EPA, 1994, 2002 and 2011; Meek et al. 1999, 2002; WHO/IPCS, 2005; EFSA, 2006) and formed the founding principle upon which ECHA basis its requirements for derivation of DNELs (ECHA GD) under the REACH Regulation.

ECETOC revisited the topic for the third time in 2010 (TR 110; ECETOC, 2010) and again reaffirmed their previous conclusions adding that the *additional interspecies AF of 2.5 for "remaining differences"* i.e. TD, as implemented in the ECHA GD, was questionable as it involves aspects of *"science policy*". They went on to recommend that "*this factor should be further investigated with data that will become available from the first-tier chemicals"* (under REACH).

The proposals made in 2003 and 2010 by ECETOC to change the 'default' AFs from 10x10 to more 'informed' AFs gained no traction in the development of the ECHA GD and associated guidance under REACH and was

subsequently challenged by ECHA during review of REACH registrations. Nevertheless, the concept of deviating from default assumptions where justified was, and still is, widely recognised and encouraged.

In the early 2000s the WHO/IPCS initiated a consultative process aimed at harmonising risk assessment approaches with the objectives of promoting 1) common understanding and encouraging the incorporation of quantitative data in the measurement of dose/concentration–response and 2) research in areas that might lead to more predictive estimates of risk and paved the way to the concept of 'Chemical-Specific Adjustment Factors' (WHO/IPCS 2005).

The concept of refining assessments through tiers of increasing sophistication was subsequently described by WHO/IPCS in 2014 in their tiered approach to risk assessment and uncertainty analysis. In this approach lower-level tiers deal with default (conservative) assumptions for both exposure and hazard with higher tiers moving from semi-quantitative to more data-derived and quantitative approaches based on increasing information on mode of action (MOA) and species concordance, increasing extent of quantitation, and probabilistic versus deterministic analyses (Meek et al., 2014a & b).

The role of CSAF is recognised by ECHA on page 28 of the R.8 guidance (ECHA, 2012) by stating that "*Preferably, the value for each individual assessment factor is based on substance-specific information"* but then go on to acknowledge that "*However, although sound in principle, in practice the approach has limitations (data are often scarce, especially toxicodynamic data, and human data) and, therefore, default assessment factors most often need to be used*."

Bhat et al., in their 2017 review paper on lessons learned from over 100 case studies using CSAF from global regulators or published literature provided some independent verification of ECHA's concern that data supporting development of CSAF are indeed scarce, particularly if you were to compare this relatively small number of available case studies with the vast number (21,319 at time of review) of unique substances registered at above 10 tpa under REACH potentially requiring DNELs to be derived.

The Bhat review also concluded that in all cases, but for some perfluorinated compounds, "*TK or TD subfactors based on chemical-specific information tended to be less than the default subfactors resulting in guidance values greater than those based on defaults"*. It should be recognised that this could reflect bias in the selection of candidate chemicals for development of CSAF i.e. selection of those identified as having the greatest likelihood of deviation, or be taken as a more general confirmation that default AFs are indeed too conservative, particularly when extrapolating from effects observed in rodents.

With regard to the implications for REACH and Chemical Safety Assessment process, then generating substance-specific information for all chemicals that require assessing on an individual chemical basis would not be a plausible option since it would be both resource and cost prohibitive. So, if indeed the combination of using default, conservative AFs with conservative exposure assessment is for the majority of substances making the process unworkable or overly restrictive, then there is a tangible impetus to develop approaches that might be able to provide the same high level of confidence in deviating from defaults based upon other considerations, such as read-across to chemicals for which CSAF have been sufficiently validated.

Whatever the terminology used, whether "Substance specific" (ECHA, 2008); "Chemicals Specific" (CSAF - WHO/IPCS,2005) or "Data-Derived"" (DDEF – US EPA, 2014), it is broadly recognised that these factors can be

derived for a single substance or chemical, or for a group of compounds (JMPR, 2006, 2007, 2008; ECHA, 2008; JECFA 2011; US EPA, 2014; Bhat, 2017) with similar MOA/AOP (Adverse outcome pathway) or common elimination pathways. What is perhaps missing, therefore, is a framework for the development and communication of these grouping and read across concepts that will allow regulators and agencies to accept them as being sufficiently justified (see section 5).

4.1 Identifying the most appropriate assessment factor to use

ECHA GD recommends that 'each step in the process (of extrapolation from experimental data to the human exposure situation), including any choice for an assessment factor value, whether substance-specific or default should be explained as transparently as possible, with a qualitative narrative in the chemical safety report (CSR)'. ECETOC concurs with this recommendation since this is essential in order to provide transparency and to optimise the likelihood of acceptance by the reviewer.

In this regard, Section R.8 of the 'Guidance on information requirements and chemical safety assessment' proposes a tiered and systematic approach for the delineation of DNELs and DMELs (Derived Maximum Exposure Limit) (ECHA, 2008):

Step 1:	Gather typical dose descriptors and/or other information on potency
Step 2:	Decide on mode of action (threshold or non-threshold) and which next step(s) to choose
Step 3-1:	Derive DNEL(s) for threshold endpoints
Step 3-2:	If possible, derive DMEL(s) for non-threshold endpoints
Step 3-3:	Follow a more qualitative approach when no dose descriptor is available for an endpoint
Step 4:	Select the leading health effect(s)

While DNEL are defined as safe exposure levels for threshold effects, such safe levels cannot be defined for non-threshold effects, e.g. effects of genotoxic carcinogens or mutagenic effects. In this case, one should calculate a DMEL which is an exposure level considered to be of 'very low concern'. Derivation of DMEL will not be addressed in this document.

The following sections give guidance on the main issues to include in derivation of the overall AF applied in the general assessment procedure for threshold endpoints. The individual factors contributing to the overall AF are described separately in the following Section.

4.2 Selection of the relevant dose-descriptor(s) for the endpoint concerned

The GD requires that DNELs are developed for each dose descriptor identified from the available data for each human health endpoints so as to identify the most sensitive or lead endpoint for subsequent use in the chemical safety assessment.

In this regard it should be noted that as confirmed during the ECHA webinar on "the latest information about ECHA's and industry's action plans for addressing the lack of compliance of REACH registration dossiers" (26th of November 2019[1]) that DNEL should not be developed for chemicals that do not present a hazard, i.e. no classifiable effects are observed e.g. at the limit dose.

4.3 Modification of the dose descriptor(s)

In some situations, the conditions under which the effects assessment was made are not directly comparable to the conditions required for the target exposure assessment i.e. in terms of exposure route, units and/or dimensions. In these situations, it is necessary to convert the dose descriptor for the threshold effect (e.g. N(L)OAEL, benchmark dose, LD/LC50) into a "corrected starting point".

ECHA GD goes on to highlight certain conditions under which modification is not appropriate. Examples include the use of human data where modification is not required, or where the effect is local as opposed to systemic or where the metabolism involves a first pass effect, in which case route-to-route extrapolation is inappropriate. It is not necessary to reproduce this detail here in which case the reader is referred to the GD.

4.4 Route-to-route extrapolation

Route to route extrapolation is desirable where sufficient, reliable data exists by one route of exposure and an assessment is required by a different route of exposure for which data is lacking. In such cases route to route extrapolation would avoid unnecessary animal testing.

According to the REACH GD (ECHA, 2012) and ECETOC (2003), route-to-route extrapolation is appropriate for systemic effects but not appropriate for substances with a local mode of action where local effects are more dependent on concentration than on dose.

ECHA REACH GD recognises in Section R.8.4.2 that "It is to be noted that route-to-route extrapolation is associated with a high degree of uncertainty and should be conducted with caution relying on expert

[1] http://echa.europa.eu/de/-/improving-the-quality-of-your-reach-registration-dossier-what-authorities-are-planning-and-how-you-can-prepare

judgment". The guidance states that substance-specific data on absorption via the different routes are to be preferred but that in the absence of these data for both the starting route and the end route (the route to which the extrapolation is being made), worst case assumptions have to be made. Worst case in this context will be obtained assuming a limited absorption for the starting route, leading to a low (conservative) internal NOAEL.

Accordingly the guidance proposes: "… thus, in the absence of route-specific information on the starting route, to include a default factor of 2 (i.e. the absorption percentage for the starting route is half that of the end route) in the case of oral-to-inhalation extrapolation. The inclusion of this factor 2 means for example that 50% (instead of 100%) absorption is assumed for oral absorption, and 100% for inhalation. Note that if data on the starting route (oral) are available these should be used, but for the end route (inhalation), the worst-case inhalation absorption should still be assumed (i.e. 100%). Note that this does not apply if there is a first pass effect, if there is non-resorption, or for bolus effects.

No default factor should be introduced (i.e. factor 1) in case of inhalation-to-oral extrapolation, because a two times higher oral compared to inhalation absorption appears on empirical grounds not justified.

On the assumption that, in general, dermal absorption will not be higher than oral absorption, no default factor (i.e. factor 1) should be introduced when performing oral-to dermal extrapolation."

ECETOC in their review in 2003 also recognised that "route-to-route extrapolation was characterised by considerable scientific uncertainty that may impact route-to-route extrapolation". In 2010, ECETOC again reviewed the state-of-science and confirmed their earlier opinion adding that "The default AF of 2 of the REACH GD for oral to inhalation extrapolation does not correspond with the evaluations carried out by the European competent authorities under the previous EU Existing Chemicals Regulation (EC, 1993; EC, 1994). Similarly, the oral to dermal extrapolation AF of 1 will very often lead to an overly conservative estimate of the POD for dermal exposure, while an AF <1 would be appropriate, although not allowed for by the present REACH Regulation (EU, 2006)".

Since it is almost a decade since the last review and considerable high reliability data has been collected under REACH in the meantime it is perhaps timely to revisit this topic to determine if the state-of-science has progressed any further.

Schröder and co-workers attempted to derive route to route extrapolation factors (EF) based on no/lowest effect levels (NOELs/LOELs) in the Fraunhofer RepDose® database for the oral to dermal or oral to inhalation route (Schröder et al., 2016). 246 paired studies (for 110 compounds) allowed analysis of oral-to-inhalation extrapolation. While the authors recognised that route-to-route (R2R) extrapolation is hampered by such factors as type of application (e.g. gavage, drinking water or food for oral studies), first pass effects, differences in absorption, metabolism, distribution, bioavailability and toxicity and despite not controlling for these in the analysis, surprisingly a relatively low EF of 2.2 (95% CI 1.2–3.1) was derived for systemic effects in inhalation studies which was taken to indicate that the uncertainty of R2R extrapolation for systemic effects is low despite these "hampering" factors. For local effects, the EF was 4.4 (95% CI 2.0–8.6), and the EF without distinguishing local or systemic effects (any EF) was 3.2 (95%, CI 1.7–5.0) and on this basis proposed that as it can normally not be estimated which type of effect will be observed in inhalation studies, that an EF of 3 seemed to be the best choice as default extrapolation factor. However, the authors concluded on this basis that the importance

of local effects for triggering low inhalation LOELs may have been overestimated (ECHA, 2012) since consistent with their previous studies (Schröder et al., 2015) they found that in only 20% of the inhalation studies analysed did local effects drive the LOEL (in 31% of studies local and systemic effects coincided, while only systemic effects were found in 41%of cases). Furthermore, it should be recognised that often is the case that additional information on irritation (skin and eye; and sometimes even acute inhalation studies) may already be available and that certainly for irritant substances, this data may inform on the contribution that local effects may make in repeated dose studies (Rennen et al., 2002, 2004).

Overall, the findings of Schröder and co-workers are consistent with current guidance (IGHRC, 2006; ECHA, 2012) that state that R2R extrapolation is not necessary for local effects but that a default AF of 2 is appropriate for oral to inhalation extrapolation for systemic effects (REACH GD; ECHA, 2012).

The dataset oral to dermal was too small to allow general conclusions, the results at that stage confirmed, however, that the current ECHA guidance appeared conservative in assuming that dermal absorption is as high as oral absorption (Schröder et al., 2016).

4.5 Exposure duration extrapolation

4.5.1 Exposure duration extrapolation; Systemic effects

Exposure extrapolation should be considered to take account of differences in the experimental exposure duration and the duration of exposure for the population and scenario under consideration. The AFs proposed by the REACH GD are sub-chronic to chronic: 2; sub-acute to chronic: 6; sub-acute to sub-chronic: 3. According to the REACH GD (Section R.8.4.3.1) these defaults should be substituted by substance-specific information that may lead to higher or lower AF.

- "A lower AF may …. be used if there is specific evidence that increasing exposure duration does not increase the incidence or severity of adverse effects……
- A higher factor may …. be used if there are indications for potential severe chronic effects which cannot possibly be detected in a short-term study."

ECETOC previously reviewed assessment factors for exposure duration both in their 2003 and 2010 reviews and concluded that differences in length of exposure should be accounted through the use of an AF. They recognised that applying a default AF assumes that effective dose levels and thresholds for saturation phenomena decrease with increasing exposure time but that this is not always the case so adding this factor may increase the level of conservatism in the DNEL calculation and this may necessitate the derivation of a substance-specific informed AF. They were of the opinion that studies with exposure duration of 6 months or longer are sufficient to identify chronic effects but confirmed the same AF for exposure duration extrapolation of systemic effects as in the REACH GD.

In the 2011 review ECETOC additionally referenced the findings of the ERASM project and their analysis of the data within the RepDose® (Bitsch et al. 2006) that at that time contained about 670 substances and 2200 studies on repeated-dose toxicity. The data demonstrated that as long as the material is soluble, the sub-acute to sub-

chronic factor was 1.5, rather than 3, the sub-acute to chronic factor was 3.4 and the sub-chronic to chronic factor was 1.4 (Batke et al, 2011).

Since 2010 more data has become available as a result of ongoing registration activity, much of this generated to support registration under the REACH regulation within Europe. Escher and co-workers extracted repeat dose data from the ToxRef[2], RepDose[3], Hess DB[4], IMI eTOX[5] and ELINCS (Kalkhof et al., 2012) databases for generation of extrapolation factors (EF) for oral administration (302 EFs for 172 chemicals - subacute-to-subchronic and 1059 for 462 chemicals - subchronic-to-chronic) and inhalation exposure (67 EFs for 44 chemicals (subacute-to-subchronic) and 226 EFs for 71 chemicals (subchronic-to-chronic) (Escher et al., 2020).

To account for recognised deficiencies and variations in the study design the impact of six differences (different points of departures (PoD); differences in dose spacing; dose selection; study quality; single dose group and absence of any effect up to the highest tested dose) on the EF distribution was investigated using the dataset subchronic-to-chronic. Most differences in study design do not have a significant impact on the mean log EFs values but some differences had an impact on the variance of the dataset. The analysis did, for example confirm their previous finding that high differences in dose spacing lead to a higher spread of the resulting EF distribution but do not have a high impact on the GM (geometric mean) values (Batke et al. 2011).

After exclusion of study pairs with high differences in dose spacing, dose selection or one dose tested, the authors concluded that mean EF for systemic effects in subchronic to chronic extrapolation was 1.5.

This factor also seems justified for the extrapolation from subacute to subchronic duration after either oral or inhalation exposure in contrast to the currently recommended EF of 3 in the GD (Escher et al., 2020). If choosing a purely deterministic approach of aggregating the variance of multiple AF, the observed variance between chemicals within the Escher 2020 dataset could be used to achieve a pre-defined coverage of 75, 90 or 95%. The inter-chemical variance was analysed in one exemplary dataset, which shows that the variance within chemicals is actually larger than variance of EF between chemicals, and that e.g. 75% coverage would be achieved by an AF of 2.7 (1.5 (GM) x 1.8 (variance factor CI 95) = 2.7). It has to be noted that, for multiple reasons, the default AF traditionally used in RA partly take account of variance, and partly not. In any case, it may be technically simpler to evaluate the AF designated to theoretically different aspects of variability and uncertainty independently, however, in practice, they are not strictly independent variables, and should be evaluated in a joint and balanced approach.

ECETOC recognises the significance of this new analysis since for the lower volume band chemicals of greater than 10tpa rarely have repeat dose studies of duration longer than sub-acute so consequently rely to a greater extent on the study duration AF than do the chemicals in the higher tiers for which longer duration studies are typically available. The previous ECETOC report TR110 already identified for chemicals in tier 1 (>1000tpa) the significant challenge that was being faced when balancing DNELS derived as a result of multiplication of

[2] https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=NCCT&dirEntryId=227139

[3] https://repdose.item.fraunhofer.de/

[4] http://www.nite.go.jp

[5] http://www.etoxproject.eu

conservative AFs with the conservative exposure predictions, derived using screening tools such as the ECETOC TRA (Tiered Risk Assessment), under the risk characterisation ratio (RCR) recommended under the REACH GD. Experience since then has demonstrated that this is even more challenging for chemicals in the subsequent tiers making the need for review of the study duration AF a priority.

ECETOC suggests that if the key study complies with modern OECD guidelines and there is high confidence in both the qualitative and quantitative aspects of the POD then EFs of 1.5 for both subacute-to-subchronic and subchronic to chronic (both oral and inhalation) without further factors should be sufficient. In contrast, if there is low confidence in the quality of the key study and/or the POD that an additional factor of between 2 and 4 should be applied.

ECETOC recognises that industry might consider using this analysis, if sufficiently documented and justified, as a basis for chemical-specific deviation from default assumption. ECETOC therefore, urges ECHA and other regulators to review the newly available data and consider updating the GD thereby avoiding divergent opinions and practices from developing.

Escher et al., did identify a general trend in which more toxic compounds showed on average an EF of 1, which is lower compared to chemicals with higher NOELs but cautioned that a better understanding on effects/mechanisms and their probability to cause lower NO(A)EL after prolonged exposure would be needed before practical application. ECETOC suggests that this may be taken into consideration when assigning any additional factor to account for study quality and confidence in the POD as indicated above.

The authors additionally investigated grouping of compounds in an attempt to distinguish significantly different EFs for groups of similar compounds but were unsuccessful. This might reflect the limited numbers of compounds and/or the way subgroups were combined so not firm conclusion on the utility of grouping and read-across should be assumed.

4.5.2 Exposure duration extrapolation; Local effects

ECHA GD recognises that adjustment for duration extrapolation, involves considerable uncertainty but nevertheless requires the same default duration factors for local effects, and in the case of toxicity testing by inhalation for local tissue damage in the respiratory tract, as for systemic effects i.e. sub-chronic to chronic: 2; sub-acute to chronic: 6; sub-acute to sub-chronic: 3.

The GD guidance does recognise that “a lower factor (minimum 1) may for instance be used if there is specific evidence that increasing exposure duration does not increase the incidence or severity of adverse effects. This applies to most local dermal effects. It is also relevant for certain local effects in the respiratory tract for which there is no substantial difference in N(L)OAECs following acute and subacute exposure by inhalation (the effects can thus be considered concentration- rather than dose-dependent)”. The ECETOC review in 2003 explained that “local effects (e.g. on the respiratory tract, but also on skin or internal organs) are related to the deposited dose per unit of surface area, i.e. concentration rather than the total dose (AUC). Below a certain concentration, the capacity of the epithelial cells to neutralise a substance is not overwhelmed. A crucial point is the definition of the threshold for cytotoxicity, e.g. by histopathology or cell proliferation. It is concluded that no additional AF is needed for substances with a local effect below the threshold of cytotoxicity for exposure duration”. The

ECETOC 2010 review looked more closely into the paper by Kalberlah et al. (2002) that ECHA cites in support of these factors as well as the paper by Kalberlah and Schneider (1998) which proposed similar numbers and other than finding "some severe deficiencies (in the NTP dataset) making it inappropriate and inadequate to draw any reliable conclusions regarding AF to account for study duration with respect to local effects" was unable to recommend alternatives.

The extended database available to Escher and co-workers was also used to investigate study duration EFs for local effects (Escher et al., 2020). Local effects were defined as any effects being observed in the organs of first contact (predominantly in the respiratory tract, but also rarely in the eye as well as "respiratory distress" as reported under clinical symptoms).

This analysis indicates that on average NOEL values of local effects decrease over time comparable to systemic effects with on average an EF of 2.1 (95% CI 0.8-5.2) for subacute-to-subchronic and 1.9 (95% CI 1.3-2.8) for subchronic-to-chronic extrapolation. These derived EFs appear consistent with the ECHA GD default duration factors of sub-chronic to chronic: 2; sub-acute to chronic: 6; sub-acute to sub-chronic: 3. However, the authors caution that the subset used for this comparison was rather small so perhaps no firm conclusion should be drawn.

Furthermore, the previous ECETOC report concluded that exposure duration extrapolation is not appropriate for transient sensory irritation, which may be responsible for respiratory distress, citing the work of Shusterman et al. (2009). The technical report explained that since the onset of sensory irritation will occur quickly, extrapolation is not appropriate. On this basis the inclusion of PODs based upon "respiratory distress" may have been inappropriate so it may be premature to draw conclusions on this data analysis. Other potential reasons why this analysis failed to support the guidance of the GD are also explored in section 5.

4.6 Interspecies extrapolation

In most situations, the species in which the effects assessment was made is not the same as the species for target exposure assessment i.e. humans. It is necessary therefore to make judgements as to how humans might respond based upon the response observed in the test species. This process is termed Interspecies extrapolation and for obvious reasons is accompanied with some uncertainty.

4.6.1 Interspecies extrapolation; Systemic effects

As stated previously, the default 10-fold uncertainty factors for interspecies differences include both toxicokinetics (TK) and toxicodynamics (TD) considerations. TK refers to those factors such as absorption, distribution, metabolism and excretion that determine the concentration of a substance within the body; while TD refers to the molecular, biochemical, and physiological effects of toxicants or their metabolites in biological systems and are result of the interaction of the biologically effective dose of the ultimate (active) form of the toxicant with a molecular target within the cell.

As with route to route extrapolation, ECHA GD would prefer the use of substance specific information over default assumptions but acknowledge that data scarcity often preclude this. This situation is echoed in guidelines issued by other agencies and authorities.

The two earlier ECETOC reviews analysed the data upon which the 10-fold factor, and the contributing TK and TD considerations, was based in order to reduce the inherent conservatism of this approach. The 2003 task force (TF) reviewed the data of (Freireich et al., 1966; Schein et al., 1979; Hattis et al., 1987, 1999a, 1999b; Watanabe et al., 1992; Calabrese and Gilbert, 1993; Hattis and Silver, 1994; Renwick, 1998; Renwick and Lazarus, 1998; Clewell et al., 2004). Particular focus was given to statistical reanalysis of the data of Freireich et al., 1966 and Schein et al., 1979 based upon the MTD (Maximum Tolerated Dose) ratios calculated by Travis and White, 1988 (table 2 in TR86) and the fact that this indicated that allometric scaling predicted reasonably well the appropriate dose in humans. They did note that the GSD (geometric standard deviation) suggested some variability or uncertainty which could be interpreted as necessitating an additional uncertainty factor, but since the analysis was based upon real human data, they considered it more likely due to a combination of differences in biological sensitivity between species and intraspecies differences. The 2007 ECETOC TF review essentially reasserted this earlier interpretation of the reanalysis of (Freireich et al., 1966; Schein et al., 1979; Travis and White, 1988) data and concluded that while the TK factor of 4 (rat to human) was justified to account for differences in allometry, the routine application of the factor of 2.5 for TD was in their opinion unjustified.

These "informed" AFs proposed by ECETOC were not recognised by ECHA as a valid deviation from the TDG (which required use of the default 10-fold factor in the absence of substance-specific data) as they were considered insufficiently justified to be regarded chemical specific and therefore contrary to the objective of REACH which is to afford a high level of protection for the consumer.

The recent review by Bhat et al., (2017) appraised all published literature as well as data submitted by eight organisations from six countries and work group members based on their institutional knowledge in response to a data call-in. It is not the purpose of this review to repeat the findings of this group other than to repeat their conclusion that all of the 100 cases they reviewed, with the exception of some perfluorinated compounds, "*TK or TD subfactors based on chemical-specific information tended to be less than the default subfactors resulting in guidance values greater than those based on defaults"* does justify revisiting this topic to determine if the state-of-science has progressed during the past 15 years.

A recent literature search has failed to reveal any significant contribution to our understanding in this area over and above that identified in the Bhat review. Therefore, in the absence of additional data justifying a general deviation, the 10-fold uncertainty factor for interspecies differences according to the GD remains the default assumption in the REACH context.

4.6.2 Interspecies extrapolation; Local effects

ECETOC in the 2010 report (TR 110; ECETOC, 2010) cites REACH GD, Section R.8.4.3.1, which states that allometric scaling should not be applied (allometric scaling factor of 1) to local effects, since they are independent of the basic metabolic rate. *"For the remaining uncertainties in kinetic (at a smaller extent) and in dynamic (at a larger extent) interspecies differences, consideration of the mechanism of toxicity is crucial, e.g.*

if the effect is a simple destruction of membranes due to the physicochemical properties (e.g. pH) of the chemical concerned as opposed to a mechanism involving local metabolism".

The TR110 report goes on to quote the GD "Given that there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and when there is no data to inform on this uncertainty, it is prudent to assume that humans would be more sensitive than animals to effects on the respiratory tract. In such a situation, a chemical-specific remaining uncertainties factor or the default factor of 2.5 should be applied, as would be the case for systemic effects." Referring back to the earlier TR 86 report (ECETOC, 2003) and the relevance of the marked morphological and aerodynamic differences between rodents (principally rats) and humans and the consequential at least 2 to 4-fold greater sensitivity of the rat nasal cavity with respect to local effects of water-soluble gases and vapours observed compared to the humans (Harkema et al., 2006).

Such approaches have been used to justify deviation from default AFs for example in the case of organic esters and acetates (Andersen et al., 2002). However, these are resource consuming to develop and therefore are likely only to be employed in cases where a lower risk characterisation ratio cannot be achieved by a refinement of the exposure assessment.

4.7 Intraspecies extrapolation

Intraspecies assessment factors are needed to account for the variability in the target population to take account of sensitive target populations such as very young children, elderly people and persons having diseases (e.g. diabetics, people with kidney diseases). In the CSA Guidance R.8 (ECHA, 2012), the reasons of intraspecies variation are listed: "Humans differ in the sensitivity to toxic insult due to e.g. genetic polymorphism, age, gender, health status and nutritional status."

4.7.1 Intraspecies extrapolation; Systemic effects

The GD (R.8.4.3.3.) (ECHA, 2012) proposes an AF of 5 for workers and 10 for the general population. As described in section 4.1 there has been a long tradition of using a factor of 10 to account for human variability (general population) in the risk assessment of chemicals from as long ago as 1954 (Lehman and Fitzhugh) and this has been adopted by most if not all national agencies. Investigations into intraspecies variability in humans have understandably been limited to the field of pharmaceuticals.

ECETOC in the 2010 report (TR 110; ECETOC, 2010) stated that in contrast to the AF for exposure duration and interspecies differences of toxicokinetics in which the AF are derived from different distribution and central estimates (50th percentile) that the choice of intraspecies variability for deriving an AF is not a science-based decision but depends on science policy and defining the desired level of coverage (conservatism). TR 110 referred to their earlier analysis (TR 86, 2003) in which AFs of 3 (workers) and 5 (general population) were derived based upon a review of the literature and especially an analysing the data of Hattis and Silver (1994), Hattis et al., (1987, 1999a & b) and Renwick and Lazarus (1998). As no new data have become available since the prior publications, it is not the objective of the present report to repeat yet again this analysis and the reader is referred to the 2003 report (TR 86; ECETOC, 2003) for full details.

It has still to be concluded that while ECETOC views its analysis scientifically valid the reality that in the absence of a much larger database on intraspecies variability within humans that the long standing practice of using the default factor of 10 for the general population (and by virtue of this the factor of 5 for the worker) is likely to remain a matter of science policy and is unlikely to change in the near future. While further data on intraspecies variability in humans is likely to only become available from the pharmaceuticals sector it should be recognised that this will be on pharmacological actives and the relevance of this to other industrial chemicals may be questioned.

Consistent with ECHA guidance and recommended practice, substance-specific deviation from default factors is recognised where information such as toxicokinetic and/or toxicodynamic information or PBPK modelling data is available and can be used to justify special assessment factors.

4.7.2 Intraspecies extrapolation; Local effects

The REACH GD recognises the limited availability of information on intraspecies variation with respect to local effects and proposes the same default AF as for systemic effects, i.e. 5 for workers and 10 for the general population. ECETOC in the 2003 report (TR 86; ECETOC, 2003) after reviewing data on respiratory irritants in human volunteers confirmed this viewpoint and this was not changed in the 2010 report (TR 110; ECETOC, 2010) other than recommending the use of its reduced AFs. Again, apart from using substance-specific factors this is regarded a matter of science policy and is unlikely to change in the near future, given the lack of a broader database of human evidence for individual differences in susceptibility which could increase confidence in more precise factors.

5. USE OF READ ACROSS TO EXTEND THE SCOPE OF APPLICABILITY OF CSAF

As recognised in section 5, the comprehensive review by Bhat and co-workers in 2017 was only able to identify a little over 100 case studies using CSAF. This likely reflects not only the specialist knowledge required to developing such models but also the high cost, both financial and in specialist resources. This inevitably leads to the conclusion that CSAF will likely only ever be developed for a small number of high-profile/value chemicals. So, if wider benefit is to be achieved from this insight and applied more widely, for example to the vast number of unique substances registered at above 10 tpa under REACH potentially requiring DNELs, then frameworks for applying this knowledge to this larger set of chemicals will have to be developed and recognised by the risk assessment community.

The use of read-across is widely accepted across regulatory jurisdictions and general practices and associated guidance are available, such as that of the OECD guidance on grouping of chemicals (OECD, 2014) and the ECHA RAAF (ECHA, 2017b). According the RAAF both the "Analogue approach" and the "Category approach" could be used to test the hypothesis that CSAF developed for a data rich "source" chemical can be read-across to relatively data poorer "target chemicals".

As identified by the OECD (2014) the concept of MOA/AOP and bioprofiling information can be used in forming/justifying chemical analogy/categories as well as the OECD toolbox and tools such as, but not limited to, EU Toxmatch[6] and US EPA Analog Identification Methodology (AIM)[7].

The finding by Escher and co-workers (Escher et al., 2020) that grouping of compounds did not reveal significantly different EFs for groups of similar compounds i.e. group-specific EFs were not supported, might be taken as evidence to discourage the development of read-across approaches. This should not be the case, however, as a case study may explain why such categorical applications of read-across may be restricted to sub-sets of similar chemicals that not only share a common MOA and/or adverse outcome pathways (AOP) leading to the POD, but also possess a set of determinant properties that result in the molecular initiating events (MIEs) or key events (KEs) essential for that AOP to be expressed. A case study may perhaps illustrate this point.

5.1 Case study on the use of read-across within a category

The category of C1 - C8 alkyl methacrylate esters (methyl, ethyl, n-butyl, iso-butyl and 2-ethylhexyl) (Gelbke et al., 2018) can be used to illustrate how read-across may be used in this regard. Volatile esters and acetates are recognised as causing toxicity in the olfactory region of the rodent nose upon inhalation (Hardisty et al., 1999). Inhalation of Methyl methacrylate (MMA) has been shown to cause destruction of the olfactory epithelium in

[6] https://ec.europa.eu/jrc/en/scientific-tool/toxmatch

[7] https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool

the upper respiratory tract of rats (Lomax et al., 1997) and studies with the carboxylesterase inhibitor bis-(p-nitrophenyl)phosphate (BNPP) have demonstrated that this is the consequence of intracellular ester cleavage to MAA, an irritant and corrosive metabolite (Mainwaring et al., 2001) leading to decreased intracellular pH. Currently only one AOP titled "Intracellular Acidification Induced Olfactory Epithelial Injury Leading to Site of Contact Nasal Tumours" (136) has been proposed[8] and although methacrylate esters including MMA have not been shown to be tumourigenic in the rodent nose (NTP, 1986; Chan et al., 1988; Lomax et al., 1997) the sequence of KEs relating to absorption and hydrolysis of the parent ester and olfactory tissue destruction by the acid metabolite are relevant in this regard. A PBPK model for MMA induced olfactory toxicity was developed and the lower sensitivity of humans when compared with rats was proposed (Andersen et al., 1999) and subsequently formed the basis for chemical specific deviation from default AFs for interspecies differences between rat and human in the derivation of a DNEL for human health risk assessment under REACH. The PBPK model showed that three key properties of MMA namely high volatility, sufficient water solubility and short ester half-life are critical in achieving optimal partitioning between air and aqueous mucous phases and rapid ester hydrolysis by carboxylesterases required for MMA's nasal toxicity. This profile is not shared by all alkyl methacrylate esters. Indeed, olfactory toxicity diminishes rapidly with increasing molecular weight across the alkyl series in line with a decrease in all three parameters such that olfactory lesions are not observed with the C8 (2-ethylhexyl ester) (Gelbke et al., 2018).

Key parameters of volatility, water solubility and ester half-life (hydrolysis by carboxylesterases) thereby could be used as a basis for defining the boundary conditions and reading across the CSAF for MMA relating to the POD of olfactory toxicity not only to other alkyl methacrylates, but potentially to other chemistries that share this AOP.

This also explains why for other alkyl methacrylates, despite sharing some aspects of structural similarity to the volatile lower alkyl esters (MMA (Methyl methacrylate) EMA (Ethyl methacrylate) and BMA (Butyl methacrylate)), do not necessarily share the same POD in repeat dose studies. Furthermore, this may explain in part why the analysis of Escher and co-workers found that the range of EFs for different groups of "similar" compounds, but with potentially with disparate key properties, overlapped so much.

It is recognised that development and application of such a read-across approach is relatively sophisticated and would be associated with new uncertainties that have little regulatory precedence upon which to base acceptance, so it would be essential to involve all stakeholders in the development of case studies and associated guidance.

[8] https://aopwiki.org/aops/136

6. DISCUSSION

This present review by ECETOC set out to revisit the findings of the previous ECETOC reviews on AFs as reported in TR 68 (ECETOC,1995), TR 86 (ECETOC,2003) and TR 110 (ECETOC,2010) and to update this guidance, if necessary, in light of new science. In the process, it became evident that a more detailed explanation of the evolution of regulatory practices and guidance surrounding AFs was necessary in order to understanding how this ECETOC guidance may be used to best effect.

The primary focus of the 2003 and 2010 ECETOC reviews was on the default factors of 10 for inter- and intra-species variability in deterministic risk assessment. The Bhat et al., (2017) review paper on 'Chemical-Specific Adjustment Factors' (CSAF) described the evolutionary timeline of the major developments surrounding the WHO/IPCS (2005) CSAF guidance and how the 'default adjustment factors' became enshrined in most regulatory practices and guidance across the world, including EU REACH. REACH guidance (R8) recognises a wide variation in approaches to setting AFs but adopted the default factors recommended by IPCS (WHO/IPCS, 2005) and widely used by other agencies to obtain a harmonised set of default factors thereby securing transparency and consistency. However, as mentioned in the REACH guidance (appendix R. 8-3), there is no firm scientific rational upon which to define default AFs and although the REACH regulation aims to "provide a high level of protection for human health and the environment" it fails to define the particular level of coverage of the population that it aims to protect (e.g. 50th percentile (= geometric mean of distribution) or 90^{th}, 95^{th} or 99^{th} percentile (i.e. P90, P95 or P99 of distribution). Here, it is important to note that the progress made by WHO IPCS (WHO IPCS, 2014) and EFSA (EFSA, 2018) in characterisation of uncertainties (including variability) has not yet been taken up sufficiently broadly into the knowledge and work of regulatory toxicologists and risk assessors, nor into REACH guidance documents. Accordingly, Bhat et al 2017 state that "Using chemical-specific information to depart from the default factor inevitably reduces uncertainty, yet this fundamental concept is not generally commonly understood and/or accepted."

Perhaps, not surprisingly, ECHA guidance in this area refers to the same publications and scientific arguments provided by ECETOC TR110 report (ECETOC, 2010) and the recent publications by Schröder and co-workers (2015, 2016). The difference between the numerical values being recommended by the two groups (ECHA R-8 GD and ECETOC TR110) on the face of it seems to reflect differences in opinion on how to interpret and combine statistical distributions to achieve overall sufficient coverage and a high level of protection. If this is indeed the case, then perhaps a first and essential step in reconciling this apparent difference would be the declaration by ECHA of the overall "level of protection" that the REACH guidance is trying to achieve. Once the level of protection is defined then science can define appropriate AFs' and appropriate statistical methods for their combination to achieve these levels of protection. This would also be a milestone towards increasing transparency and reducing uncertainty in risk assessments under REACH. In the absence of this development the current task force concludes that the difference between the numerical values being recommended by the two groups rather reflects differences in interpretation of statistical data and that there is not a strong scientific justification for the widely recognised overall AF of 100 (10x10). However, there is currently insufficient scientific support within the regulatory community to replace these "defaults" with the "informed" ECETOC factors outlined in the T110 report. As such the use of the overall AF of 100 can be regarded as a matter of science policy and it must be recognised that in the context of the REACH regulation, ECHA sets the policy.

Consequently, if "informed" ECETOC factors are to be used then registrants will have to meet the requirement for transparent, scientific justification of these to the satisfaction of ECHA.

In contrast, the AFs used to account for differences in study duration represent an area for advancement of the science and policy since there has been recent and significant developments in the underlying science. In this regard, the recent publication by Escher and co-workers while supporting the existing extrapolation factor (EF) for differences in study duration in the GD for local effects indicate that deviation from the currently recommended EFs of 3 for sub-acute to sub-chronic and 2 for sub-chronic to chronic respectively in the GD is justified for systemic effects (Escher et al., 2020). Recognising the greater variability of the dataset observed due to inclusion of lower quality (e.g. non-guideline) studies, ECETOC suggests that if the key study complies with modern OECD guidelines and there is high confidence in both the qualitative and quantitative aspects of the POD then EFs of 1.5 for both subacute-to-subchronic and subchronic to chronic (both oral and inhalation) without further factors should be sufficient. In contrast, if there is low confidence in the quality of the key study and/or the POD that an additional factor of between 2 and 4 should be applied.

Chemicals in the lower volume registration band of greater than 10tpa rarely have repeat dose studies of duration longer than sub-acute and these also tend to rely on conservative exposure assessments which could lead to excessive conservatism. Therefore, review by ECHA of the study duration AF would appear to be highly recommended.

While development of CSAF are encouraged over use of default AFs, it is recognised by ECHA and WHO IPCS that this practice is extremely resource demanding and likely only limited to more established chemicals. In this regard there is some promise for using "read-across" technology between relatively data poor chemicals and CSAF data sets for more established chemicals. However, the approaches have to be transparent and scientifically valid. ECETOC recognises that while this practice is not widely used and guidance is lacking on how this might be done, the RAAF developed by ECHA (2017b) based upon WHO guidance may provide a useful framework.

Finally, during the preparation of this report other factors were identified that while being outside of the scope of the current AF review would benefit from further discussions. One such example was the recent proposal discussed at the Meeting of Competent Authorities for REACH and CLP (Classification, Labelling and Packaging) (CARACAL) (EC, 2020) to apply a Mixture Assessment Factor (also called Mixture Attribution Factor) under REACH Annex I, as part of the mandatory DNEL or PNEC (Predicted No-effect Concentration) derivation for substances to account for the fact that any registered substance under REACH may eventually contribute to the combined daily exposure of humans and the environment. Alternatively, the factor could also be applied to the Risk Characterisation Ratio (RCR). A further example was the recognition by ECHA that DNEL should not be developed for chemicals that do not present a hazard, i.e. no classifiable effects are observed e.g. at the limit dose.

ABBREVIATIONS

AFs: Assessment Factors
AIM: Analog Identification Methodology
AOP: Adverse outcome pathway
AUC: Area Under Curve
BMA: Butyl methacrylate
BNPP: bis-(p-nitrophenyl) phosphate
BOELV: Binding occupational exposure limit value
CLP: Classification, Labelling and Packaging
CSAF: Chemical Specific Assessment Factors
CSR: Chemical Safety Report
DG EMPL: Directorate-General for Employment, Social Affairs and Inclusion
DMEL: Derived Minimal-Effect Level
DNEL: Derived No-Effect Level
ECHA: European Chemicals Agency
EF: Extrapolation factors
EMA: Ethyl methacrylate
ERASM: Environmental & Health Risk Assessment and Management
GD: Guidance document
GM: Geometric Mean
GSD: Geometric Standard Deviation
IOELV: Indicative occupational exposure limit value
KEs: Key events
LC50: Lethal Concentration, 50%
LD: Lethal Dose
LD50: Lethal dose, 50%
LOAEL: LOw Adverse Effect Level
LOELs: Lowest Effect Levels
MIEs: Molecular initiating events
MMA: Methyl methacrylate
MoA: Mode of action
MTD: Maximum Tolerated Dose
NMP: N-methyl-2-pyrrolidone
NOAEL: NO Adverse Effect Level
NOELs: No Effect Levels
NTP: National Toxicology Program
OEL: Occupational or workplace exposure limits
PBPK: physiologically based pharmacokinetic
PD: Pharmacodynamic
PNEC: Predicted No-effect Concentration

POD: Point of departure
RAAF: Read-across assessment framework
RAC: Risk assessment committee
RCR: Risk characterisation ratio
REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals
R2R: Route-to-Route
SCOEL: Scientific Committee on Occupational Exposure Limits
TD: Toxicodynamics
TF: Task Force
TK: Toxicokinetics
TRA: Tiered Risk Assessment
UFs: Uncertainty factors
WoE: Weight of evidence

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www.ecetoc.org
D-2021-3001-262

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