The ECETOC TRAv3.1 and ECHA Technical Guidance ChR15v2016

Since the release of the ECETOC TRA v3.1 in 2014, ECHA released an updated version of Chapter R15 Guidelines for Consumer Exposure Assessment in August 2016 (referred to here as R15v2016). This version of Chapter R15 recognizes the difficulty of comparing infrequent and/or short duration exposure estimates to a long-term systemic DNEL value. It is well recognized that the duration and frequency of exposure and hazard should be aligned in order to combine the two into a risk estimate. Similar to the approach of the TRA, R15v2016 proposed adjustment factors that can be applied when comparing exposure estimates to long term DNELs for calculation of RCRs. The approaches differ, however, in the considerations in determining these factors and the exact numeric factors used. In order for the user to best assess how the TRA should be applied for a particular assessment, information as to the basis of each approach and how they compare is provided here. The TRA approach for developing the adjustment factors is based upon adjusting the exposure estimate to match the hazard benchmark, whereas the R15v2016 approach is based upon adjusting the hazard benchmark to match the exposure estimate. In this respect, frequency and duration need to be approached separately and then combined, as in some cases infrequent uses may have short durations.

TRA

As a default, all scenarios in the TRA assume a frequency of daily use (or multiples uses per day in the case of air fresheners). Thus, no frequency adjustments are applied in the default-based version of the TRA. Refinements offered by Specific Consumer Exposure Determinants, however, include consideration of frequency. In order to fully utilize the information value of the SCEDs, the TRA includes the option to implement a frequency banding that accounts for Low Frequency Events (see Table 1 below taken from ECETOC Technical Report 124, 2014).

Table 1: Categories for infrequent consumer use

Frequency of Use	Definition	Proposed TRA Multiplier	Rationale for Multiplier
Frequent	Event occurs at least once a week.	1	Equates to daily use
Occasional	Event occurs between once a week and once a month.	0.2 (5x)	Exposure reduction factor reflects the fact that average exposures are expected to be at least one order less than daily exposures
Infrequent	Event occurs between once a month and once every 6 months.	0.04 (25x)	Exposure reduction factor reflects the fact that average exposures are typically expected to be at least 50 fold less than daily exposures
Very Infrequent	Event occurs no more than once in 6 months.	0.01 (100x)	Exposure reduction factor reflects the fact that average exposures are expected to be at least two orders less than daily exposures

This approach is based upon that employed by other 'gold standard' consumer exposure models, e.g. ConsExpo, E-FAST, where long term average daily doses are estimated by considering the frequency of occurrence per year. The day of use exposure is multiplied by the frequency per year and then divided by the number of days per year for an annual average. The TRA stops at the annual average; it does include calculation of a Lifetime Average Daily Dose (LADD) as found in some models, in which the annual average is then further reduced by multiplying by (the number of years in which exposure occurs divided by the years in a lifetime. As Table 2 indicates, the TRA factors for calculation of annual averages are similar or more conservative than the values that would be applied if the actual frequency was used. It should also be noted that use of a conservative estimate for the frequency itself (based upon higher end of frequency range) provides a starting point that is already meant to be conservative (and hence consistent with a Tier 1 model), especially for products that are not likely to be used on an annual basis (some DIY products for example).

This approach is valid for substances where effect is related to the total exposure (Concentration X Duration) as compared to the peak concentration i.e. they follow Haber's Law. There are some substances, however, where Haber's Law does not follow and for which this approach may not apply. To assist in appropriate application of this feature in the TRA tool, domains of use are provided (see Inset 1).

Table 1 above provides the adjustment factors both as the values that could be applied to the exposure estimate (values <1) and the reciprocal values which would be the equivalent counterparts used if it was preferred to adjust the DNEL rather than the exposure value.

Table 2 Comparison of TRA frequency band values with frequency of use

Frequency of Use	Frequency (days/year)	Factor if used actual frequency (days per year/365)	TRA Band factor/Actual Use frequency Factor
Frequent	52 – 365	0.14 – 1	1 – 7
Occasional	12 – 52	0.03 – 0.14	1– 6
Infrequent	2 – 12	0.005 – 0.03	1 – 7
Very Infrequent	1 – 2	0.003 – 0.005	2-4

Technical Guidance ChR15v2016

Alternatively, R15v2016 proposes an approach that adjusts the DNEL value for infrequent exposures, but also indicates that for pragmatic purposes the exposure estimate could be adjusted by the reciprocal of this value for the RCR.

Table 3 REACH ChR15v2016 DNEL adjustment factors

Frequency	Adjustment Factor – Multiply DNEL by	Reciprocal factor if applied to exposure
>=15 days/year	1	1
<15 days/year	6	0.17

How to use the TRA to derive an estimate based upon the R15v2016 factors:

A) TRA event values (no application of frequency banding) could be:
   a. Compared to DNELs that are multiplied as per Table 3
   b. Multiplied by the reciprocal factor in Table 3 and then compare to the Long Term Systemic DNEL

B) For TRA values estimated with frequency banding implemented (application of SCEDs), the banding exposure estimate OR RCR calculated based upon the banded exposure could be multiplied by the factors as shown if it is desired to have a value consistent with R15v2016 guidance.

Table 4 comparison of TRA frequency band values with frequency of use

Frequency of use	TRA factor	R15 reciprocal factor (if applied to exposure estimate)	R15/TRA	TRA Scenarios
52 – 365	1	1	1	Default for all TRA scenarios = daily use (4X/day air fresheners)
15 - 52	0.2	1	5	
12 – 15	0.2	0.17	0.85	
2 – 12	0.04	0.17	4.2	
1 - 2	0.01	0.17	17	

Comments on the Use of Haber's Law

Inset 1.

Domains of Use:

The TRA was developed as a screening level exposure and risk assessment tool.

TRA develops exposure and risk estimates based upon the event exposure. The event exposure is expressed on a mg/kg/day basis for dermal and oral routes, and mg/m3 concentration for the event duration for inhalation. The event values are compared to long term systemic DNEL values.

The TRA includes a feature where for infrequent exposures (< 1/week) an adjustment factor can be applied to reduce the exposure estimate for comparison to the long term systemic DNEL. A user of this feature should take into account the following application boundaries:

1. Substances beyond Haber's Law should be excluded, such as:
    - Substances with non-steady state, non-linear kinetics
    - Genotoxicants
    - Immune reaction promoting chemicals (sensitizers or autoimmunity inducers)
    - Reactive chemistry (degree of reactivity may be important)
2. In addition, triggers for substance-specific assessment as to the suitability of infrequent exposure adjustment include:
    - Long half-life of elimination (weeks to years)
    - Substances for which a toxic metabolite is produced only under conditions of high exposure
    - Corrosive or irritating substances (degree of irritation may be important), or physical hazards (flammability)
    - Chemicals with portal of entry effect and chronic DNEL based upon alternate exposure route (but should have an acute DNEL)
    - Developmental hazard potential identified or expected
    - Non-genotoxic carcinogenic hazard identified