



# IMPACT OF DATA AVAILABILITY ON THE CALCULATION OF REACH DNELs FOR WORKER AND CONSUMER POPULATIONS

Robert Roy, Nathan Pechacek, Lawrence Milchak, and Robert Skoglund  
3M Company, Medical Department, St. Paul, Minnesota

Abstract  
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## ABSTRACT

Under the European Union's Registration, Evaluation, Authorization, and restriction of Chemicals (REACH) regulation, the Derived No-Effect Level (DNEL) represents a level of exposure above which humans should not be exposed. Chemical-specific DNELs for worker (W-DNEL) and consumer (C-DNEL) populations are often derived as part of the chemical safety assessment. The European Chemicals Agency (ECHA) has developed guidance for the calculation of DNELs for both workers and consumers. Steps in DNEL calculation include establishing study "dose descriptor(s)" such as NOAEL, LOAEL, etc. and their modification for bioavailability, route-to-route extrapolation and exposure conditions; and, lastly, application of Assessment Factors (AFs) for intra- and inter-species differences, duration of exposure, etc. While it is preferable to use chemical-specific modifiers/factors in DNEL calculations, many are not readily available and, thus, ECHA provides default factors for use in these calculations.

The impact of both chemical- and use-specific data (vs. defaults) is illustrated by calculating W-DNEL and C-DNEL for: (1) long-term inhalation exposure based on rat inhalation data and (2) long-term dermal exposure based on oral rat data. Significant differences in W-DNEL and C-DNEL values can be observed depending on the use of chemical-specific data (e.g. dermal and oral absorption data for route-to-route extrapolation) and consumer use data (e.g. number of hours/day of exposure). For example, if both dermal and oral % absorption of a chemical is known, the use of these data can provide a significantly different DNEL vs. the DNEL calculated using ECHA defaults. As an example of case (2), above, the DNEL for a chemical with 100% and 10% absorption via oral and dermal routes, respectively, will be 10-fold greater than that calculated using the ECHA defaults. This exercise shows the importance of using reliable, available, chemical-specific data for calculation of DNELs for use in REACH compliance.

## THE DNEL IN REACH RISK CHARACTERIZATION

The DNEL is a critical element of the risk characterization process for REACH-regulated chemicals. The DNEL is used in calculating the Risk Characterization Ratio (RCR):

$$RCR = \frac{\text{[known or modeled] Exposure Concentration}}{DNEL}$$

If Exposure < RCR → risk is adequately controlled (RCR < 1)  
If Exposure > RCR → risk is not adequately controlled (RCR > 1)

## MODIFICATION DOSE DESCRIPTORS FOR DNEL CALCULATION

ECHA Guidance (ECHA, 2008) states that it is sometimes necessary to modify the selected dose descriptor(s) (e.g. NOAEL, LOAEL, etc.), for each selected effect endpoint, to a correct starting point in cases where there may be differences in: (1) Bioavailability of the chemical between experimental animals and humans for the same route of exposure; (2) Route of exposure in the experimental study vs. that of the defined human exposure pattern; (3) Human and experimental animal exposure conditions; and (4) Respiratory volumes between

experimental animals at rest and humans during light activity. For (1), the ECHA default is to assume, in the absence of any data, the same bioavailability for experimental animals and humans for a particular exposure route. For (4), the dose descriptor modification is only needed when a "worker" DNEL, for the inhalation route of exposure, is being derived. In this case, the ECHA default modifier is 0.67 (respiratory volume of experimental animals at rest =  $6.7 \text{ m}^3 \div 10 \text{ m}^3$  = respiratory volume of workers during light activity). The remainder of this poster will focus on the use of chemical-specific and exposure-specific data for (2) and (3), respectively, for the modification of dose descriptors for DNEL derivation.

For (2), route-to-route (RtR) extrapolation can be done if there are no adequate experimental data available for systemic (but not local) health effects on the relevant route of exposure for the human population (e.g. workers, consumers, etc.) under consideration. RtR extrapolation is considered appropriate only under certain conditions (ECHA, 2008; TGD, 2003). The need to do RtR extrapolation of a dose descriptor from an oral exposure study to one applicable to the dermal route of exposure has been found to be fairly common in the derivation of DNELs because many experimental animals studies are done via the oral route of exposure and these data often are needed for the derivation of DNELs for human populations exposed via the dermal route. ECHA Guidance assumes that, in general, dermal absorption will not be higher than oral absorption and thus a default factor of "1" should be used for oral to dermal RtR extrapolation. ECHA provides the following equation (Eq. 1) for this RtR extrapolation:

$$\text{[corrected] Dermal NOAEL} = \text{Oral NOAEL} \times \frac{\text{ABS}_{\text{oral}} - \text{rat}}{\text{ABS}_{\text{dermal}} - \text{human}}$$

For (3), since exposure conditions for animal studies often differ from that for the human population under consideration, this must be taken into consideration in DNEL derivation. For example, inhalation studies in experimental animals are often 6 hours/day while ECHA considers exposure duration for workers to be 8 hours/day, 24 hours/day for humans exposed via the environment and 1-24 hours/day for consumers (depending on the exposure scenario). ECHA provides the following equations for modification of the dose descriptor for exposure duration for workers and consumers:

*Workers (Eq. 2):*

$$\text{[corrected] Inhalation NOAEL} = \text{InhalationNOAEL} \times \frac{\text{ExposureConditions}_{\text{Rat}} \left( \frac{\text{hr/day}}{\text{hr/day}} \right) \times \frac{6.7 \text{ m}^3}{10 \text{ m}^3}}{\text{ExposureConditions}_{\text{Human}} \left( \frac{\text{hr/day}}{\text{hr/day}} \right)}$$

*Consumers (Eq. 3):*

$$\text{[corrected] Inhalation NOAEL} = \text{InhalationNOAEL} \times \frac{\text{Exposure Conditions}_{\text{Rat}} \left( \frac{\text{hr/day}}{\text{hr/day}} \right)}{\text{Exposure Conditions}_{\text{Human}} \left( \frac{\text{hr/day}}{\text{hr/day}} \right)}$$

## EXAMPLE CALCULATIONS – WORKER AND CONSUMER DNEL

### Inhalation Experimental Animal Data → Inhalation DNEL

DNELs for the human exposure pattern of Inhalation/Long-Term Exposure/Systemic effects will be calculated using data from a 90-day rat inhalation study (6 hr/day) with NOAEL = 125 mg/m<sup>3</sup>.

**Worker:** The modification of the dose descriptor is done using Eq. 2:  $125 \text{ mg/m}^3 \times 6 \text{ hr}/8 \text{ hr} \times 0.67 = 63 \text{ mg/m}^3$ . Applying default ECHA assessment factors (AFs) to this value gives a DNEL =  $2.5 \text{ mg/m}^3$  ( $63 \text{ mg/m}^3/25$ ).

**Consumer:** Eq. 3 is used to modify the dose descriptor. However, now the known or expected duration of consumer exposure to the chemical must be considered. The numerator is set at 6 hours (based on the study) but, as ECHA states, the consumer can be exposed for 1-24 hours, depending on the exposure scenario. One could use a default consumer exposure duration = 24 hours which would give a modified dose descriptor of  $31 \text{ mg/m}^3$  ( $125 \text{ mg/m}^3 \times 6 \text{ hr}/24 \text{ hr}$ ). In using this default exposure of 24 hours, one is assuming continuous consumer exposure; however, this may be considered unrealistic and an assessment of a more realistic consumer exposure duration may provide a much more realistic (and defensible) DNEL. For example, a more realistic default (in the absence of actual duration measurements which may, if needed for many similar consumer exposure scenarios, be very difficult and time-consuming) may come from consumer exposure duration data assembled for multiple types of consumer products (e.g. DIY products, paint products, cleaning products, pest-control products, etc.) contained in ConsExpo Fact Sheets (RIVM, 2006-2007). The Fact Sheets provide exposure durations (e.g. accounts for exposure occurring during product use/application and if the consumer stays in the area/room after the task) for a wide range of general consumer product categories as well as products themselves. An informal analysis of these exposure data found an exposure duration range for consumer products of approximately 10 minutes to 480 minutes (8 hours) with most exposures generally falling in the range of 240 minutes (4 hours) or less. Therefore, if deemed appropriate, one could use a "default" consumer duration exposure significantly less than 24 hours (if actual consumer exposure duration data are not available). Using Eq. 3, the following consumer inhalation DNELs were calculated for exposure durations of 4, 6, 8, and 12 hours (note in all examples, the ECHA default AFs were used to give a total AF = 50):

Consumer Exposure Duration	NOAEL	Exposure Duration Adjustment	AF	DNEL
4 Hours	125 mg/m <sup>3</sup>	6 hr/4 hr	50	3.75 mg/m <sup>3</sup>
6 Hours	125 mg/m <sup>3</sup>	6 hr/6 hr	50	2.5 mg/m <sup>3</sup>
8 Hours	125 mg/m <sup>3</sup>	6 hr/8 hr	50	1.8 mg/m <sup>3</sup>
12 Hours	125 mg/m <sup>3</sup>	6 hr/12 hr	50	1.25 mg/m <sup>3</sup>
24 Hours	125 mg/m <sup>3</sup>	6 hr/24 hr	50	0.625 mg/m <sup>3</sup>

Example calculation (6 hr):  $125 \text{ mg/m}^3 \times (6 \text{ hr}/6 \text{ hr}) \div 50 = 2.5 \text{ mg/m}^3$

Therefore, one can see that using a more realistic consumer exposure duration (vs. a default of 24-hour continuous consumer exposure) can have a significant effect on the resulting inhalation DNEL.

### Oral Experimental Animal Data → Dermal DNEL

DNELs for the human exposure pattern of Dermal/Long-Term Exposure/Systemic effects will be calculated using data from a 90-day rat oral study with NOAEL = 750 mg/kg-day.

**Worker Example 1:** RtR extrapolation (using Eq. 1) will be used to modify the dose descriptor (oral NOAEL) in order to derive the dermal DNEL. In this example, the ECHA default of 100% absorption by both the oral and dermal route will be used (i.e. a Tier 1, conservative assessment) to derive a corrected dermal NOAEL:  $750 \text{ mg/kg-day} \times 100\%/100\% = 750 \text{ mg/kg-day}$ . Applying ECHA default AFs would give a dermal DNEL =  $7.5 \text{ mg/kg-day}$  ( $750 \text{ mg/kg-day} \div 100$ ).

**Worker Example 2:** In this example, further investigation of the toxicokinetics of the test chemical revealed that its oral absorption in the rat was 90-100% and the dermal absorption in humans was actually 40-50%. Again using Eq. 1, a more-refined (corrected) dermal NOAEL can be calculated:  $750 \text{ mg/kg-day} \times 90\%/50\% = 1,350 \text{ mg/kg-day}$ . Applying ECHA default AFs would give a dermal DNEL =  $13.5 \text{ mg/kg-day}$  ( $1,350 \text{ mg/kg-day} \div 100$ ).

**Consumer Example:** For the consumer dermal DNEL calculations, the only difference from the two worker calculations is that the total default AF would be 200 (vs. 100 for the worker). Using this AF would give consumer dermal DNELs of 3.75 mg/kg-day (vs. 7.5 mg/kg-day) and 6.75 mg/kg-day (vs. 13.5 mg/kg-day).

Using these simple examples, the significant impact of the incorporation of chemical-specific absorption data (when available) on the resulting dermal DNEL is apparent.

## SUMMARY

The DNEL, as part of the RCR calculation, plays a critical role in the human health risk characterization process. Thus, the derivation of sound, scientifically defensible DNELs is one critical element essential for REACH compliance.

The examples provided in this poster illustrated ways in which the incorporation of actual (or more refined) use information (i.e. duration of consumer exposure to REACH-regulated chemicals or to products that contain them) and absorption data (oral and dermal absorption for use in RtR extrapolation), vs. the use of sometimes conservative default inputs, can have a significant impact on DNEL derivation.

## REFERENCES

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