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Interpreting REACH guidance in the determination of the derived no effect level (DNEL)

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ABSTRACT

Under the new European chemicals regulation, REACH, a new safety value, the Derived No Effect Level (DNEL) must be established for all chemicals manufactured, imported or used in the EU in quantities greater than 10 metric tonnes per year. The DNEL is to be calculated for all relevant exposure pathways, exposure populations, and endpoints of toxicity. The EU has published guidance on how to derive the DNEL, but this guidance has yet to be put into practice and is in some places not prescriptive. Using the Agency for Toxic Substances and Disease Registry (ATSDR) dataset, we have determined inhalation DNELs for styrene. In doing so, we considered what effect key decisions would have on the calculated DNEL. The resulting DNELs were then compared to existing risk criteria values or occupational exposure limits. General population DNELs were generally more conservative than analogous risk criteria (ranging from approximately 0.05 to 2.5 ppm). Worker DNELs are lower than existing occupational standards (ranging from approximately 0.4 to 20 ppm). To our knowledge, this work represents the first rigorous application and interpretation of the EU guidance for determination of a DNEL and will prove useful as a model for determination of other DNELs under REACH.

1. Introduction

Under the new European chemicals regulation, REACH (Registration, Evaluation, Authorization and Restriction of Chemicals), the chemicals industry is obligated to register all chemicals imported or produced in the European Union (EU) in volumes exceeding 1 tonne per annum (tpa) (EC, 2006; Williams et al., 2009). Many of the almost 150,000 chemicals identified during pre-registration may undergo the rigorous steps of completing a registration dossier. As part of the registration dossier for substances manufactured or imported in quantities greater than 10 tpa, registrants must submit a Chemical Safety Report (CSR) to demonstrate for all uses of a chemical, potential risks to human health or the environment can be adequately controlled (EC, 2006; ECHA, 2009; Williams et al., 2009). In order to demonstrate safety, exposure estimates for each identified use will be compared to screening criteria values, as is typically done in the context of the risk assessment paradigm (EC, 2006; Williams et al., 2009; Williams and Paustenbach, 2002).

For REACH, a newly developed health benchmark, the Derived No Effect Level (DNEL), is required in order to conduct this risk characterization. A DNEL is required for all chemicals manufactured or imported at 10 tpa or greater and the details of its derivation are to be reported as a part of the CSR (EC, 2006; ECHA, 2008b; Williams et al., 2009). The CSR will document a broad risk assessment process by identifying the potential hazard to human health, quantifying exposure through exposure scenarios, and then characterizing the risk by comparing the estimated exposure to the DNEL. Recommendations for determination of DNELs are offered in the guidance on information requirements and chemical safety assessment in Chapter 8 (characterisation of dose [concentration] – response for human health) (EC, 2006; ECHA, 2008b; Williams et al., 2009). A basic flowchart describing the method for determining the DNEL and the role of the DNEL in the risk characterization is found in Fig. 1 (ECHA, 2008a). An appropriate DNEL is required for all anticipated exposure scenarios, and therefore a variety of values may be necessary, including different values based on: route of exposure, location of effect (local or systemic), exposed population (worker or general population), exposure duration (acute or repeated dose toxicity), and where applicable, toxicological endpoint (e.g., reproductive or developmental toxicity) (ECHA, 2008b). The development of this type of screening criteria value to be used in risk characterization is somewhat different than that recommended in previous EU guidance, which advocates a margin of safety (MOS) approach in risk characterization (ECB, 2003).

While DNELs will be required for thousands of chemicals, for some as early as 2010, there has been no published application

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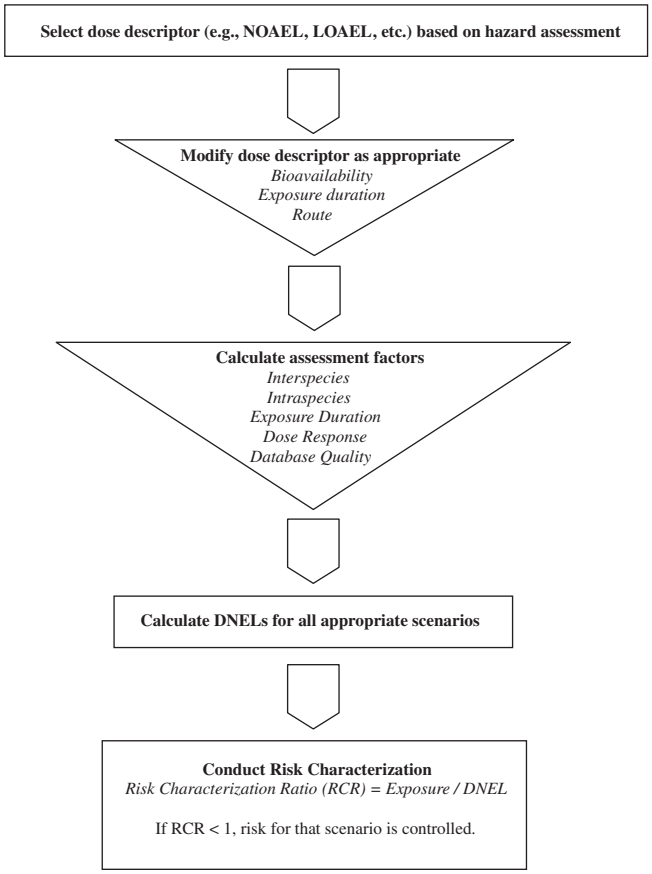

Fig. 1. Flow diagram of process for generating DNEL and use of DNEL in risk characterization. Adapted from Fig. B.7-1 of guidance on information requirements and chemical safety assessments part B: hazard assessment (ECHA, 2008a).

of the recommended guidance (ECHA, 2008b). Gade et al. (2008) discuss the use of DNELs to determine safety for preparations, but the methodology they employ to arrive at DNELs for each component is not discussed (Gade et al., 2008). The guidance is, in some places, vague and lacking in prescriptive instructions, and therefore establishment of DNELs will rely on expert judgment. The goal of the work presented here was to apply the guidance to a toxicity dataset for a well-characterized chemical and compare resulting DNELs with analogous health benchmarks for other regulating bodies (e.g., occupational exposure limits, reference doses [RfDs], etc.) in order to more fully understand the methodology advocated by the European Chemicals Agency (ECHA).

Because the Agency for Toxic Substances and Disease Registry (ATSDR) toxicity profile for styrene has recently been updated (2007), we selected styrene as the chemical of interest (ATSDR, 2007). Styrene is most commonly used for the manufacture of polystyrene plastics or resins, the production of styrene-containing copolymers, or the manufacture of styrene-butadiene rubber (ATSDR, 2007; ECB, 2001). Styrene is a high production volume chemical, with EU production volumes ranging between approximately 2 and 5 million tonnes per annum. Further, an additional 30,000–150,000 tpa are imported into the EU (European Chemicals Bureau, 2001). Therefore, styrene falls into the highest tonnage band under REACH, hence requiring the most information and detail in the registration dossier regarding toxicity, exposure, and subsequently risk (EC, 2006; ECHA, 2008c).

In this work, we followed the REACH guidance for determination of DNELs to calculate DNELs for styrene. Where there was ambiguity in the REACH guidance, or where professional judgment warranted deviation from the guidance, our decision making process in determining DNELs for styrene is discussed. We considered the impact that key decisions (e.g., selection of method to adjust dose to represent population, selection of dose descriptor, etc.) had on the outcome and compared calculated DNELs to analogous health benchmarks (e.g., Reference Concentrations (RfCs), occupational standards, etc.).

2. Methods

As stated previously, in this work we applied the REACH guidance for determining DNELs (see Fig. 1 for stepwise description of process) to the toxicity dataset for styrene, as provided in the recently updated ATSDR toxicological profile (ATSDR, 2007). Not included, however, is an analysis of data quality and validity or a search for supplemental toxicity data, steps that would be required under REACH (ECHA, 2008b). Such additional analysis is outside of the scope of the purpose of this study. However, it is worth noting that guidance for preparation of Toxicologic Profiles by ATSDR lists a number of desirable attributes of studies to be considered, including peer-review, support of findings from other investigations, similarity of results with tests on similar compounds, adherence to GLP, and minimal use of subjective information. Several of these criteria overlap with those described for data quality evaluation for the purposes of REACH. This dataset included 168 dose descriptors (e.g., NOAELs, LOAELs, LD50s, etc.) from which the DNELs were calculated. Because the primary path of exposure to styrene is through inhalation for both the general and working population, we only determined DNELs for inhalation in order to limit the scope of this work, although oral and dermal DNELs will be required to comply with REACH for populations where those pathways represent reasonable routes of exposure (ATSDR, 2007). In order to determine what impact species selection had on the outcome, we calculated DNELs based on both animal and human data, where possible. The following represents the basic equation used to determine the DNELs:

$$\mathrm{DNEL} = \frac{\mathrm{DD_{Adj}} \times \mathrm{MF1} \times \mathrm{MF2} \times \mathrm{MF3}\ldots}{\mathrm{AF1} \times \mathrm{AF2} \times \mathrm{AF3}\ldots}$$

Such that: $\mathrm{DD_{Adj}}$ = adjusted dose descriptor (see Section 2.1.1); MF = modifying factors; AF = assessment factors.

ECHA default modifying or assessment factors were used unless otherwise noted (Table 1). The product of the modification factors and the adjusted dose descriptor ($\mathrm{DD_{Adj}}$), which is a term defined by the authors, results in the corrected dose descriptor ($\mathrm{DD_{corr}}$) as referred to in the guidance (ECHA, 2008b). Based on the available data in the ATSDR dataset, inhalation DNELs were calculated for the following combinations: chronic systemic toxicity, acute systemic toxicity, chronic local toxicity, acute local toxicity, chronic eye irritation, and acute eye irritation. It is anticipated that, the more sensitive endpoint between local and systemic toxicity will drive the selection of the DNEL for each the chronic and acute exposure scenarios; however, for the sake of completeness, calculations were made for all combinations of exposure duration and location of toxicity (Williams et al., 2009). Although eye irritation is not an effect mediated through inhalation, exposure to vapor phase styrene provides the underlying data for this DNEL, and therefore it was included along with studies of inhalation of vapor phase styrene.

No DNELs were calculated for reproductive or developmental toxicity, as there is no evidence in the ATSDR dataset that these effects occur in response to styrene (ATSDR, 2007). Also, no mode-of-action determinations were made for potential carcinogenic effects of styrene. According to REACH guidance, non-threshold toxicity (e.g., mutagenic carcinogenicity) should be characterized

Table 1
Summary of modifying and assessment factors used in calculation of DNELs for styrene.

Factors	Condition	Value used – systemic effects	Value used – local effects
Modifying factors			
Bioavailability adjustment	Rodent study	0.83*	1
	Human study	1	1
Route to route extrapolation	–	1	1
Exposure duration adjustment	For general population	1	1
	For workers	4.2*	4.2
Allometric scaling	–	1	1
Assessment factors			
Interspecies extrapolation	Metabolic rate per body weight (allometric scaling)	1*	N/A
	Remaining differences	2.5	1 or 2.5 depending on MOA
Intraspecies adjustment	Worker	5	5
	General population	10	10
Exposure duration	Subacute to subchronic	3	3
	Subchronic to chronic	2	2
	Subacute to chronic	6	6
	Chronic to chronic	1	1
	Acute to acute	1	1
Dose–response	Reliability of dose–response including extrapolation from LOAEL to NOAEL	1 (NOAEL); 3 (LOAEL)	1 (NOAEL); 3 (LOAEL)
Database quality	Completeness and consistency of available data	1	1

The modifying factors are those specific to the calculations performed here; those with asterisks do not, represent the defaults provided in the guidance. The modifying factor for exposure duration adjustment differs from the guidance because all dose descriptors were converted to equivalent continuous doses prior to calculation of DNELs; thus no adjustment was required for the general population and conversion back to exposure equivalent to 8 h per day, 5 days per week was required to calculate worker DNELs. Route to route extrapolation adjustment is not necessary as only inhalation studies were considered in this exercise. All assessment factors listed in the table are the defaults provided by the guidance. MOA – mode of action.

using a Derived Minimal Effect Level (DMEL) (ECHA, 2008b). There is a single inhalation study within the ATSDR dataset indicating that styrene may cause bronchoalveolar carcinoma in mice (Cruzan et al., 2001). However, the weight of evidence on styrene mutagenicity and carcinogenicity is not strong. Styrene is characterized as a category 2B carcinogen (no evidence in humans, limited evidence in animals) by the International Agency for Research on Cancer (IARC) while the American Conference of Governmental Industrial Hygienists (ACGIH) has determined there is inadequate evidence to characterize the carcinogenicity of styrene (ACGIH, 2006; IARC, 2002). Further, mode-of-action investigations implicate the role of reactive oxygen species and cytotoxicity in causing lung tumors from styrene exposure suggesting that styrene genotoxicity may occur through a threshold mode of action that may not be applicable to humans (Cruzan et al., 2009, 2001; Harvilchuck and Carlson, 2009; Harvilchuck et al., 2009). Based on this evidence, the dataset employed for this exercise did not warrant the determination of a DMEL for carcinogenicity, though the authors recognize the possibility that information required for registration may provide additional mode of action information that would necessitate the calculation of such a value.

Once the DNELs were determined, they were compared to analogous existing health benchmarks already in place. A search was conducted to identify exposure limits for both the general population and workers, and where possible, for both acute and chronic exposure scenarios. Sources such as the International Toxicity Estimates for Risk Assessment (ITER) database, the ACGIH Guide to Occupational Exposure Values, and the California Office of Environmental Health Hazard Assessment Reference Exposure Level database were consulted to obtain a variety of health benchmarks for styrene (ACGIH, 2006; OEHHA, 2010; TOXNET).

2.1. Key decisions and deviations from guidance

As the guidance, at times, required expert interpretation in determining the appropriate steps of the DNEL calculation process, professional judgment was required to make key decisions affected the outcome of the task at hand. We deviated from the guidance on two points: selection of appropriate dose descriptor based on toxicity dataset; and adjustment of dose based on bioavailability differences between test species and exposure population (humans). A brief description of how we arrived at these decisions that deviated from the guidance follows below.

2.1.1. Selection of appropriate dose descriptor

Although the selection of the dose descriptor is the most important factor in determining the final DNEL, the method for selecting the appropriate dose descriptor is not well described in the guidance. In traditional dose response assessment, such as that described in the US EPA's "A Review of the Reference Dose and Reference Concentration Process," the point of departure from which the screening criteria will be derived should be based on values that most closely approximate the threshold for the effect (US EPA, 2002). Therefore, when evaluating a variety of data points, including NOAELs (No observed adverse effect levels) and LOAELs (Lowest observable adverse effect levels), the following general rules are applied:

- When using a NOAEL to derive the screening criteria value, the value closest to, but less than, the identified LOAEL should be used (for the most sensitive species).
- When using a LOAEL to derive the screening criteria value, the lowest value should be used.

The REACH guidance does not specify this methodology; rather it is somewhat unclear in the best method for selecting the dose descriptor. The Regulation and the guidance advise the selection of "key studies", and identification of a "leading health effect (i.e., the toxicological effect that results in the most critical DNEL." Further, for selecting the point of departure for the key effect, the guidance states, "If there are several studies addressing the same effects from which different NOAELs could be derived, normally the lowest relevant value should be used in DNEL derivation" (ECHA, 2008b). This recommendation mirrors that of the Technical Guidance on Risk Assessment, published by the European Chemicals Bureau, in describing the EU recommended methods for

dose response assessment (ECB, 2003). However, it is not clear what constitutes a "relevant value," thus making this instruction somewhat confusing. Because the method as described in the US EPA guidance represents the most appropriate approach for approximating a threshold for an effect, we chose to adopt this interpretation in calculating the DNELs (US EPA, 2002). In order to implement this approach, however, all NOAELs and LOAELs need to be based upon equivalent dosing regimens, such that they are comparable. As such, we converted all NOAELs and LOAELs to doses equivalent to that which would occur should the same cumulative dose be applied in over a continuous dosing regimen. This step is not detailed in the guidance but is necessary for accurately identifying the critical effect. The adjusted dose descriptor (DD_{Adj}) was then selected from the resulting values based on the above criteria. The following equation was used to determine this adjusted dose:

$$DD_{ADj} = DD \times \left(\frac{ED}{24}\right) \times \left(\frac{EF}{7}\right)$$

Such that: DD = selected dose descriptor (NOAEL or LOAEL); ED = exposure duration (h/day); EF = exposure frequency (days/week).

In the absence of more specific information for studies of occupational exposure, exposure duration and frequency were assumed to be 8 h per day and 5 days per week, in accordance with a typical work week.

Although this step represents a key decision in that it is an interpretation of unclear text in the guidance, no efforts to compare the result of this decision with alternative interpretations were made as with other key decisions. This step represents the most scientifically defensible approach for selecting a critical effect and therefore alternative methods are not considered justifiable.

2.1.2. Adjusting for differences between species and exposed population

Previous EU guidance (e.g., Technical Guidance for Risk Assessment) did not specify adjustments to the N(L)OAEL prior to risk characterization; rather the N(L)OAEL was compared directly to the exposure concentration to predict the MOS. Uncertainty (such as interspecies extrapolation) is considered qualitatively following the risk characterization step (ECB, 2003). However, according to the REACH guidance, in order to extrapolate between animal studies and human exposure scenarios, it is necessary to adjust the dose descriptor (e.g., N(L)OAEL) accordingly. Typically, for an animal inhalation study, factors such as inhalation rate, tidal volume, and/or blood to air partition coefficients are considered to extrapolate doses to humans (Rees and Hattis, 1994; US EPA, 2002). Under the REACH guidance, the default approach for considering bioavailability is to assume that the test species and exposure population are equivalent (set the default equal to 1). However, it is recommended that, in the presence of more informative data, appropriate adjustment values may be used (ECHA, 2008b). The US EPA also makes recommendations for adjusting for differences in species (US EPA, 2002). For inhaled gases, there are two methods for adjusting between species: allometric scaling (which considers differences in body weight and inhalation rates) and use of blood to air partition coefficients of each species to determine an appropriate scaling factor (US EPA, 2002). The recommendation for gases like styrene (category 3 gases) is to use the ratio of blood to air partition coefficients (test species to human) to generate the scaling factor (Abraham et al., 2005; Rees and Hattis, 1994; US EPA, 2002). Further, the REACH guidance specifically states that allometric scaling should not be applied when determining a DNEL based on inhalation data. (ECHA, 2008b) Therefore, we chose to apply the EPA recommended method for category 3 gases to adjust for dose differences for species. The blood to air partition coefficient for styrene is approximately 40 for rodents and 48 for humans (Csanády et al., 1994; Dills et al., 1993; Gargas et al., 1989). Therefore, the bioavailability modification (see Table 1) we used was 0.83.

In addition to adjusting for differences in bioavailability, the REACH guidance recommends an adjustment of inhalation rate based on level of activity (e.g., worker inhalation rate is greater than general public) (ECHA, 2008b). However, as styrene is categorized as a category 3 gas, the impact of inhalation rate on exposure is negligible; the more important determinant for exposure is the rate of absorption into the blood stream from the airspace (e.g., blood to air partitioning) (Abraham et al., 2005; Rees and Hattis, 1994; US EPA, 2002). Therefore, no adjustments to inhalation rates were made in determining the worker DNELs. In the authors' opinion, this represents the best science with respect to the calculation of DNELs for category 3 gases.

3. Results

The results of the DNEL calculations using the methods described above are summarized in Table 2. The DNELs arising from the most sensitive endpoint for the chronic exposure scenario are based on evidence of local respiratory effects, specifically hyperplasia of the respiratory epithelium in mice, although these DNELs are very close to those derived based on evidence chronic systemic toxicity (Cruzan et al., 2001). For acute toxicity, the DNELs generated based on systemic toxicity (namely, reported neurological effects in humans) are lower than any other acute toxicity endpoints for styrene (Odkvist et al., 1983; Seeber et al., 2004).

As discussed in the methods, the default approach for adjusting for differences in bioavailability between the test species and humans is to assume there is no difference. Our approach, however, was more conservative by applying a factor of 0.83 to the treated dose to account for differences in blood to air partition coefficients between rodent species and humans. Use of the default approach (not adjusting for differences in bioavailability) would increase all DNELs by a factor of 1.2. In contrast the guidance recommends making an adjustment for worker DNELs to account for increased respiratory rate during light activity, as is typical when conducting occupational exposure assessments. However, because styrene is a category 3 gas (a gas with relatively low water solubility), inhalation rate is not the primary determinant of absorption/exposure (Abraham et al., 2005; ECB, 2003; Rees and Hattis, 1994). Therefore, this adjustment is not appropriate for gases with hydrophobic properties. However, had this adjustment been made, the worker DNELs would be lower by a factor of 0.33.

To compare to analogous standards, the lowest DNEL for the appropriate exposure scenario (e.g., acute versus chronic) was selected to offer the point of comparison. Table 3 shows the comparison of the DNELs to the analogous health benchmarks. As other standards do not typically differentiate based on health endpoint (e.g., local effect, systemic effect, developmental or reproductive effect, etc.), the lowest applicable value was chosen for comparison purposes. In nearly every case, for both general population and occupational exposures, the DNEL is lower than the compared benchmark (ACGIH, 2006; TOXNET). The greatest disparity is between the worker DNELs and their analogous standards. The lowest worker DNEL for chronic exposures is 50–250 times lower than 8 h TWA standards, such as the OSHA Permissible Exposure Limit (PEL), the ACGIH Threshold Limit Value (TLV), the NIOSH Recommended Exposure Limit (REL), and the German Maximum Workplace Concentration (MAK; Maximale Arbeitsplatz Konzentration). Similarly, the most conservative short-term DNEL, too, is far lower than analogous short-term exposure limits (typically 15 min limits) by a factor of approximately 15–80.

Table 2
Results of DNEL calculation grouped by type of study and test species.

Endpoint	Exposure duration	Species	Basis for dose descriptor	DD_{Adj} (ppm)	DNEL (ppm)		DNEL (mg/m^3)	
					GP	Worker	GP	Worker
Systemic toxicity	Chronic	Animal	Based on NOAEL from subchronic mouse study; neurological effects at doses above NOAEL (Cruzan et al., 1997)	10.7	0.059	0.50	0.25	2.13
		Human	Based on NOAEL from worker population; neurobehavioral effects at doses above NOAEL (Chia et al., 1994; Kishi et al., 2001)	0.95	0.095	0.80	0.40	3.41
	Acute	Animal	Based on NOAEL from mouse study; neurobehavioral effects at doses above NOAEL (DeCeaurriz et al., 1983)	69	2.3	19.3	9.80	82.21
		Human	Based on NOAEL; neurological effects (inhibition of vestibular-oculomotor system at doses above NOAEL) (Odkvist et al., 1983; Seeber et al., 2004)	2.9	0.29	2.5	1.24	10.65
Local toxicity, respiratory	Chronic	Animal	Based on LOAEL from chronic mouse study, epithelial hyperplasia in respiratory tract at LOAEL (Cruzan et al., 2001)	3.6	0.05	0.40	0.21	1.70
		Human	No identified effect level	NA	NA	NA	NA	NA
	Acute	Animal	Based on NOAEL from mouse study, nasal epithelial necrosis at doses above NOAEL (Cruzan et al., 2001; Green et al., 2001)	10	0.4	3.36	1.70	14.31
		Human	Based on NOAEL; nasal irritation at doses above NOAEL (Stewart et al., 1968)	13.5	1.4	11.3	5.96	48.13
Local toxicity, eye	Chronic	Animal	Subchronic mouse study; eye irritation in rodents at doses above mouse NOAEL (Cruzan et al., 2001; Cruzan et al., 1997)	28.5	0.48	4	2.04	17.04
		Human	No identified effect level	NA	NA	NA	NA	NA
	Acute	Animal	No identified effect level	NA	NA	NA	NA	NA
		Human	NOAEL; eye irritation at doses above NOAEL (Stewart et al., 1968)	13.5	1.35	11.4	5.75	48.56

Basis for dose descriptor represents the details regarding the study which provided the NOAEL or LOAEL from which the DNEL was generated. All studies listed as bases for acute DNELs employ acute (single dose) exposure regimens. For chronic DNELs, the treatment duration is specified (e.g., subacute, subchronic, chronic). The conversion factor for converting between mg/m3 and ppm for styrene is 4.25 mg/m^3/ppm.

Table 3
Comparison of DNELs to analogous standards (ACGIH, 2006; TOXNET).

Standard	Value (mg/m^3)	Effect at toxicity threshold
General population standards		
Chronic exposure		
US EPA RfC	1	Nervous system effects
CalEPA inhalation REL	0.9	Nervous system effects
ATSDR inhalation MRL	0.85	Nervous system effects
Health Canada TC	0.092	Nervous system effects
RIVM TCA	0.9	Nervous system effects
Calculated DNEL	0.21	Local respiratory effects
Acute exposure		
CalEPA REL – acute	21	Eye and respiratory irritation
ATSDR MRL – acute	8.5	Nervous system effects
Calculated DNEL	1.24	Nervous system effects
Worker population standards		
Chronic exposure (8 h TWAs)		
OSHA PEL	426	Narcosis
ACGIH TLV	85	Nervous system effects and irritation
NIOSH REL	213	Nervous system effects
MAK	86	NA
Calculated DNEL	1.7	Local respiratory effects
Acute exposure (STELs)		
OSHA ceiling limit	852	Tremor
ACGIH STEL (15 min)	170	Nervous system effects and irritation
NIOSH STEL (15 min)	426	Nervous system effects
Calculated DNEL	10.6	Nervous system effects

The effect at the toxicity threshold represents the effect upon which the standard was generated. DNEL values represent lowest of calculated applicable DNELs. All standards are converted to mg/m^3 for ease of comparison. NA – not available; US EPA RfC – United States Environmental Protection Agency Reference Concentration; CalEPA REL – California Environmental Protection Agency Recommended Exposure Limit; ATSDR MRL – Agency for Toxic Substances and Disease Registry Minimum Risk Level; Health Canada TC – Health Canada Tolerable Concentration; RIVM TCA – Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health and the Environment, the Netherlands) Tolerable Concentration in Air; OSHA PEL – Occupational Safety and Health Administration (US) Permissible Exposure Limit; ACGIH TLV – American Conference of Governmental Industrial Hygienists Threshold Limit Value; NIOSH REL – National Institute of Occupational Safety and Health (US) Recommended Exposure Limit; MAK – Maximale Arbeitsplatz Konzentration (Maximum Workplace Concentration, Germany); STEL – Short-Term Exposure Limit.

4. Discussion

The purpose of this work was to demonstrate and interpret the REACH guidance for deriving the health benchmark, the DNEL, which is a required step for fulfilling the registration requirements of REACH for many chemicals. It has become clear through this exercise that the guidance is neither simple nor straight-forward, and therefore expertise in the field of dose response assessment is necessary for completing this portion of the registration dossier. This is especially true with the selection and adjustment of the dose descriptor. Dose descriptor selection has the greatest impact on the DNEL values and prescriptive guidance on this step is lacking.

In this work, the authors' knowledge of traditional dose response assessment practices informed the decision making where there was deviation from or interpretation of the guidance. First, in selecting the dose descriptor, we selected the point of departure based on the value which is judged to most closely predict the threshold for the effect. Alternative interpretations of the guidance, which reads "the lowest relevant value should be used in DNEL derivation," may lead to selection of dose descriptors which are far lower than the toxicity threshold, and thus more conservative than is necessary. For example, if a dataset includes multiple NOAELs from different studies, selection of the lowest NOAEL may lead to an inappropriately conservative DNEL, as NOAELs are defined by the specific doses used in a given study. The method described here avoids this overly conservative approach by selecting the dose-adjusted NOAEL that most closely predicts the threshold of the effect (closest to the LOAEL).

To avoid dependence upon the doses used in a given study, a second option is to apply the benchmark dose methodology to a dataset. The benchmark dose method allows for use of the full dose response curve to predict the true threshold of the effect and therefore eliminates dependence upon the actual doses used in the key studies (Crump, 1984; Travis et al., 2005). This method is acceptable for REACH, but was not selected as the preferred method under this assessment because the raw data for all key studies were not available.

Based on this exercise, the method described in the REACH guidance results in the generation of health benchmarks that are more conservative than other currently existing health benchmarks. Most notably, the DNELs for the worker population are far lower than existing occupational standards, including those European in origin (e.g., the German MAK). The method for developing Occupational Exposure Levels (OELs) is not standardized across organizations, and sometimes even within organizations (Nielsen and Øvrebø, 2008; Schenk et al., 2008). Typically, OELs are set by a scientific committee of relevantly qualified individuals that is responsible for reviewing the literature related to a particular chemical and selecting a threshold for exposure based upon that data. While uncertainty or safety factors are often applied to the threshold exposure to provide a safe limit, these safety factors are often smaller than in the traditional dose response assessments conducted for general population exposures (Nielsen and Øvrebø, 2008). A review of the various approaches used for establishing OELs indicated that safety factors are not systematically applied in a routine manner.

In both the United Kingdom and Germany, human NOAELs that have been judged to be good and reliable are used as OELs, without the application of additional uncertainty factors (DFG, 2009; Fairhurst, 1995; Nielsen and Øvrebø, 2008). Uncertainty factors applied to NOAELs or LOAELs from animal studies are variable depending on the quality and type of study and the severity of the adverse effect; however, the total uncertainty is unlikely to exceed 10 unless the effect is severe (e.g., reproductive or developmental toxicity), there is a particularly sensitive population, or the underlying point of departure is a LOAEL (DFG, 2009; Fairhurst, 1995; Nielsen and Øvrebø, 2008). In contrast, the minimum uncertainty applied to the dose descriptor using the defaults from the REACH guidance is 12.5 (based on the minimum assessment factors that could be relevant for a given study as listed in the guidance), while the maximum is 1575 (based on the use of maximum assessment factors possible as listed in the guidance, including an allometric scaling factor). Further modifications to the dose descriptor, such as adjustments for bioavailability differences or route to route extrapolation, may further decrease the DNEL relative to other existing OELs. It is these inherent differences in methodology that will provide differences between existing OELs and what will be the newly developed DNELs.

The only existing occupational standards which are accepted under REACH are the European Indicative Occupational Exposure Limit Values (IOELVs), of which there are only 102 (ECHA, 2008b). While it is anticipated that the method for establishing DNELs will result in significantly lower values than the existing standards, a recent review of occupational exposure limits from 18 sources indicated that the EU IOELVs are actually, on average, higher than OELs set by other regulating communities. Only the United States OSHA had, on average, higher exposure limits than the EU for the chemicals investigated in this study (Schenk et al., 2008). Therefore, the method used to derive IOELVs may actually be less conservative than methods used to determine OELs by other governments or organizations, including the UK and Germany. As a result, ECHA's decision to accept IOELVs in lieu of the DNEL represents a logical inconsistency in what methodology is acceptable for setting occupational standards.

The REACH guidance does suggest that consideration of other existing standards is acceptable, but that if the methods in deriving those standards differ from the DNEL method, adjustments must be made accordingly (ECHA, 2008b). Because there are so few IOELVs available for use under REACH, the DNEL method may be de rigeur for the large majority of chemicals undergoing the registration process. As a result, industry may be required to demonstrate compliance with much lower occupational limits than they are currently equipped to meet (e.g., monitoring methods, engineering controls, etc.). While the DNEL is not intended to be a metric for compliance (like occupational exposure standards are), companies must demonstrate that their workers are exposed at levels below the DNEL in order to be able to place their product or products on the European market. Therefore, in effect, the DNEL will supplant all other European standards for worker exposure. This could result in significant effort on the part of industry to demonstrate they can meet these new standards.

5. Conclusions

As the registration process for REACH gets underway, the implementation of the REACH guidance for determining DNELs will be put into practice. The purpose of this work was not to provide final DNELs for styrene, but rather to develop DNELs for a chemical with a robust dataset to demonstrate how the method works and what the ultimate outcome is in relation to similar already-existing standards. As this exercise shows, the method prescribed in the guidance generally results in more conservative screening criteria values than currently exist, especially with respect to worker DNELs. The impact that this new regulation may have on industry with respect to demonstrating safe conditions for their workers has the potential to be substantial.

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