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SUBJECT: Evaluation of the Michigan Department of Environmental Quality's derivation of Initial Threshold Screening Levels for inhalation exposure to PFOA and PFOS

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This memorandum is written in response to a request from the Division of Air Quality (DAQ) for the Division of Science and Research (DSR) to evaluate the Michigan Department of Environmental Quality's (MDEQ) approach for calculating Initial Threshold Screening Levels (ITSLs) for inhalation exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). ITSLs are analogous to inhalation Reference Concentrations (RfCs).

DSR toxicologists have reviewed the MDEQ approach and recommend the default approach of applying a scaling factor (70 kg/20 $m^3$) to PFOA and PFOS oral Reference Doses (RfDs) to calculate inhalation RfCs. While MDEQ used the USEPA RfDs of $2 \times 10^{-5}$ mg/kg/day for both PFOA (USEPA, 2016a) and PFOS (USEPA, 2016b) as the basis for their ITSLs, DSR recommends that the NJDEP PFOA RfD of $2 \times 10^{-6}$ mg/kg/day and the PFOS RfD of $1.8 \times 10^{-6}$ mg/kg/day be used as the basis for NJ RfCs for these two per- and polyfluoroalkyl substances (PFAS). As you know, these RfDs were recommended by the NJ Drinking Water Quality Institute (DWQI, 2017, 2018) and accepted by NJDEP.

Background information about the MDEQ approach for calculating ITSLs for PFOA and PFOS, DSR's evaluation of this approach, and the rationale for DSR's recommendations are discussed below.

**Background – the Michigan Department of Environmental Quality's Derivation of Initial Threshold Screening Levels for PFOA and PFOS**

In 2018, MDEQ calculated ITSLs for PFOA (MDEQ, 2018a) and PFOS (MDEQ, 2018b). For PFOA and PFOS, MDEQ calculated ITSLs of 0.07 $\mu g/m^3$ for each.

In calculating these ITSLs, MDEQ used a default method of route-to-route extrapolation pursuant to Michigan Rule 232(1)(b):

$$ITSL = RfD \times (average\ body\ weight) \div (inhalation\ rate\ per\ day) \times unit\ conversion$$

Where:

- RfD is expressed in mg/kg
- Average body weight = 70 kg
- Inhalation rate = 20 $m^3$/day
- Unit conversion is expressed in 1000 µg/mg

In regard to calculating RfCs from RfDs, MDEQ (2018a) stated[1]:

> An ITSL (analogous to an RfC) can be derived from an RfD if portal of entry effects (e.g., respiratory tract effects) are not expected at the toxicologically relevant dose-range, first pass[6] concerns, and systemic absorption via the lung is likely.

In response to this statement, MDEQ (2018a) provided the following rationale to justify the use of the default route-to-route extrapolation approach:

> PFOA is expected to be a particulate, is not known to be rapidly metabolized by the liver, and is readily absorbed via the inhalation pathway (Kennedy et al., 1986, Hinderliter et al., 2006).

With this justification for the default approach, MDEQ calculated ITSLs of 0.07 $\mu g/m^3$ for both PFOA (MDEQ, 2018a) and PFOS (MDEQ, 2018b). As mentioned above, these ITSLs were based on the USEPA RfDs for PFOA and PFOS of 2 x $10^{-5}$ mg/kg/day for each compound.

*Alternative approaches for calculating the ITSLs*

In addition to this default approach, MDEQ (2018a) acknowledges that route-to-route extrapolation should be based on chemical-specific empirical data, and that the use of such data would be preferable to the default approach. MDEQ (2018a) identified the Hinderliter et al. (2006) study that investigated the relationship between inhalation and oral PFOA exposure based

[1] The footnote in the quotation from MDEQ (2018a) stated: "The first pass effect (also known as first-pass metabolism or pre-systemic metabolism) is a phenomenon of chemical metabolism whereby the concentration of a chemical is greatly reduced before it reaches the systemic circulation. This first pass through the liver thus greatly reduces the bioavailability of the chemical via the systemic circulation."

on an internal dose metric (i.e., plasma PFOA concentrations). In doing so, Hinderliter et al. (2006) conducted nose-only, aerosol exposures in male rats at 0 (air control), 1, 10, or 25 mg/m$^3$ PFOA for 3 weeks (6 hours/per at 5 days per week, excluding weekends). Before and after each exposure, blood plasma samples were taken from the rats for PFOA analysis. After the 3-week exposure period, Hinderliter et al. (2006) reported that plasma PFOA levels had reached steady state and that exposure to 1, 10, or 25 mg/m$^3$ PFOA resulted in plasma PFOA levels of 8, 21, or 36 µg/mL, respectively. Hinderliter et al. (2006) also reported that these plasma PFOA levels of 8, 21, and 36 µg/mL correspond to plasma levels resulting from total oral PFOA doses of 0.27, 0.96, and 2.0 mg/kg in rats. Based on these data, Hinderliter et al. (2006) state that "it is predicted that a 1 mg/kg oral dose produces the same PFOA blood level as a 10 mg/m$^3$ inhalation exposure in rats."

Using this ratio as a route-to-route adjustment factor, MDEQ calculated an alternative PFOA ITSL using the USEPA PFOA RfD:

$$Alternative\ ITSL = RfD \times Route\ Adjustment\ Factor \times unit\ conversion$$

$$Alternative\ ITSL = (0.00002\ mg/kg) \times (10\ mg/m^3) \div (1\ mg/kg) \times (1000\ \mu g/mg)$$

$$Alternative\ ITSL = 0.2\ \mu g/m^3$$

However, as noted in MDEQ (2018a), the route adjustment factor is not constant and varies at different exposure levels (Table 1). From the data provided by Hinderliter et al. (2006), this ratio appeared to decrease as the oral dose decreased. For perspective, the USEPA (2 x $10^{-5}$ mg/kg/day) and DWQI (2 x $10^{-6}$ mg/kg/day) RfDs for PFOA are 4 to 5-orders of magnitude lower than the lowest oral dose (0.27 mg/kg/day) reported in Hinderliter et al. (2006). This calls into question the validity of using this alternative approach based on a fixed ratio (1 mg/kg oral dose:10 mg/m$^3$) as a route-to-route adjustment factor.

Table 1. Summary of PFOA exposure data

| Inhalation (mg/m$^3$) | Oral (mg/kg) | Ratio | Plasma PFOA levels (µg/mL) |
|---|---|---|---|
| 1 | 0.27 | 3.7 | 8 |
| 10 | 0.96 | 10.4 | 21 |
| 25 | 2.0 | 12.5 | 36 |

Note: PFOA inhalation and plasma levels were measured in Hinderliter et al. (2006). Oral PFOA doses were reported but not measured in Hinderliter et al. (2006).

To account for this dose-dependent change in the inhalation concentration to oral dose ratio, MDEQ (2018a) conducted a regression analysis in order to refine the conversion of oral doses to inhalation concentrations. By plotting the inhalation concentrations and oral doses reported in Hinderliter et al. (2006) in Excel, MDEQ (2018a) determined a regression equation of a second order polynomial trendline that could be used to determine an ITSL based on a known RfD:

$$y = 2.603x^2 + 7.3457x$$

Where:

- x is the RfD
- y is the ITSL (or RfC)

Using this regression equation, the USEPA PFOA RfD of 2 x $10^{-5}$ mg/kg/day, and the unit conversion of mg to µg (1 to 1000), MDEQ (2018a) calculated an alternative ITSL of 0.15 µg/$m^3$ (rounded to 2 significant figures).

Table 2 compares the three options MDEQ (2018a) used for deriving a PFOA ITSL.

Table 2. Comparison of ITSLs (RfCs) calculated by MDEQ (2018a) using the USEPA PFOA RfD

| *Candidate ITSL (µg/$m^3$)* | *Calculation method* | *Scaling factor* |
|---|---|---|
| 0.07 | Default, Rule 232(1)(b) | 70 kg/20 $m^3$ |
| 0.2 | Hinderliter et al. (2006) | 10 mg/$m^3$ = 1 mg/kg |
| 0.15 | Polynomial trendline | $y = 2.603x^2 + 7.3457x$ (y = ITSL; x = RfD) |

Of these options, MDEQ (2018a) ultimately chose the default approach for calculating the ITSL of 0.07 µg/$m^3$. This decision is based on a lack of transparency in how Hinderliter et al. (2006) derived the relationships between oral PFOA dose and plasma PFOA concentration, and plasma PFOA concentration and inhaled PFOA concentration. Specifically, the source of the oral PFOA doses reported in Hinderliter et al. (2006) was not cited. Although MDEQ (2018a) was able to deduce that an unpublished DuPont report (Kemper and Jepson, 2003) informed the ratio reported in Hinderliter et al. (2006), MDEQ (2018a) stated that it was still unclear how Hinderliter et al. (2006) derived the relationship between inhalation and oral exposures using plasma PFOA concentrations.

In addition to calculating the ITSL for PFOA, MDEQ (2018a) also stated that:

> If PFOA and perfluorooctanoic sulfonate (PFOS, CAS No. 1763-23-1) are co-emitted, then the proposed emission rates should be evaluated together, such that the impacts of PFOA and PFOS combined shall be less than or equal to 0.07 $\mu g/m^3$ with a 24-hr averaging time, for Rule 225 applicability.

**Evaluation of the Michigan Department of Environmental Quality's Approach for Deriving Initial Threshold Screening Levels for PFOA and PFOS**

DSR toxicologists agree with the default approach (i.e., applying a scaling factor of 70 kg/20 $m^3$) used by MDEQ (2018a) for deriving an ITSL (or inhalation RfC) from an oral RfD. The NJDEP oral RfDs for PFOA and PFOS should be used as the basis for NJDEP inhalation concentrations for these PFAS.

As noted by MDEQ (2018a), toxicokinetic and toxicodynamic differences between oral and inhalation exposures must be accounted for in order to conduct route-to-route extrapolation. The toxicokinetics of PFOA (i.e., absorption, distribution, metabolism, and excretion) appear to be similar for the oral and inhalation routes of exposure. In terms of toxicodynamics, while respiratory effects have been observed with acute inhalation exposures to high concentrations of PFOA (as reviewed in ATSDR, 2018), inhalation exposure causes similar toxicities as oral exposure, such as liver and developmental effects (as reviewed in ATSDR, 2018; USEPA, 2016a). Taken together, these toxicokinetic and toxicodynamic similarities are supportive of route-to-route extrapolation based on USEPA guidance (USEPA, 1994, section 4.1.2; USEPA, 2009, section 4.2).

As discussed above, the MDEQ (2018a) derived two alternative ITSLs for PFOA. These alternative derivations were based on empirical data for plasma PFOA concentrations from inhalation exposure, as reported in Hinderliter et al. (2006). As described by MDEQ (2018a), some of the conclusions of Hinderliter et al. (2006) regarding the relationship between inhaled PFOA concentration and oral PFOA dose appear to be based on information found in an unpublished report by DuPont (Kemper and Jepson, 2003). Although the alternative approaches used by MDEQ (2018a) were transparent and DSR could reproduce the alternative ITSL derivations, DSR acknowledges the ambiguity regarding the oral PFOA doses presented in Hinderliter et al. (2006).

As part of its evaluation of the alternative MDEQ (2018a) ITSL approaches, DSR toxicologists obtained the unpublished DuPont report (Kemper and Jepson, 2003) but could not ascertain how Hinderliter et al. (2006) derived a relationship between inhaled PFOA concentration and oral PFOA dose. DSR concurs with the MDEQ (2018a) conclusion regarding the vague methodology used by Hinderliter et al. (2006) to bridge inhalation and oral exposure.

**Recommendation for Deriving RfCs for PFOA and PFOS**

Of the three approaches presented in MDEQ (2018a) for deriving a PFOA ITSL, DSR toxicologists recommend the default approach of applying a scaling factor of 70 kg/20 $m^3$ to an appropriate RfD for deriving a RfC. DSR toxicologists judge the default approach to be technically sound, as toxicokinetic and toxicodynamic differences between inhaled and oral PFOA exposures appear to be minimal. Although the method for deriving an ITSL from a RfD was illustrated by MDEQ (2018a) using PFOA, the same approach was used for PFOS by MDEQ (2018b). While the inhalation exposure database for PFOS is limited (USEPA, 2016b), it is assumed that toxicokinetic and toxicodynamic differences between inhalation and oral PFOS exposure will also be minimal. As such, DSR also recommends the default approach of applying a scaling factor of 70 kg/20 $m^3$ to an appropriate PFOS RfD for deriving a PFOS RfC.

As discussed above, the two alternative approaches presented in MDEQ (2018a) are based on a conclusion with an ambiguous basis. As such, DSR toxicologists do not currently recommend these alternative approaches. However, as these alternative approaches are based on empirical data, these approaches could be re-visited if appropriate data become available.

In deriving RfCs, DSR toxicologists recommend the use of the NJDEP PFOA RfD of 2 x $10^{-6}$ mg/kg/day (2 ng/kg/day) and the PFOS RfD of 1.8 x $10^{-6}$ mg/kg/day (1.8 ng/kg/day) that were recommended by the NJ Drinking Water Quality Institute (DWQI, 2017, 2018).

Based on these recommendations, the RfCs would be calculated as:

$$RfC = RfD \times (average\ body\ weight) \div (inhalation\ rate\ per\ day) \times unit\ conversion$$

$$PFOA\ RfC = (2 \times 10^{-6} mg/kg/day) \times (70\ kg) \div (20\ m^3) \times (1000\ \mu g/mg)$$
$$= 0.007\ \mu g/m^3$$

$$PFOS\ RfC = (1.8 \times 10^{-6} mg/kg/day) \times (70\ kg) \div (20\ m^3) \times (1000\ \mu g/mg)$$
$$= 0.006\ \mu g/m^3$$

As noted above, MDEQ (2018a) included language for when PFOA and PFOS are co-emitted. Under such scenarios, proposed emission rates for the total concentration of both PFAS would be evaluated by MDEQ. In that case, the MDEQ ITSL for the total concentration of PFOA and PFOS would be less than or equal to 0.07 µg/mL. This is consistent with the USEPA recommendation that the USEPA Drinking Water Health Advisories (USEPA, 2016c), which are based on the USEPA RfDs used in the MDEQ ITSLs, be applied to the total concentration of PFOA and PFOS.

Although PFOA, PFOS, and other PFAS are known to co-occur in some media (e.g., NJ public water supplies), the potential for additive toxicity of PFOA and PFOS was not considered in the development of the NJDEP RfDs for these two PFAS. As such, DSR toxicologists recommend that the individual RfCs for PFOA and PFOS be used to evaluate levels of these PFAS in the air, and they do not recommend the use of a singular RfC for the combined concentration of PFOA and PFOS in cases where both PFAS are emitted together.

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