MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for N-Methyl pyrrolidone (CAS No. 872-50-4)

FROM: Robert Sills, Toxics Unit Supervisor, Air Quality Division

SUBJECT: ITSL Basis

DATE: October 10, 2017

The Initial Threshold Screening Level (ITSL) for N-Methyl pyrrolidone (NMP) is 5,600 ug/m^3 with a 24 hour averaging time (AT). This represents a change from the previous ITSL of 700 ug/m^3 (annual AT).

The previous ITSL of 700 ug/m^3 (annual AT) was based on a 2-year rat inhalation bioassay with a free-standing NOAEL at 400 mg/m^3, 6 hrs/day, 5 days/week (Lee et al., 1987). The ITSL was derived from this NOAEL with time adjustment and a total uncertainty factor (UF_T) = 100.

The present assessment utilized recent literature reviews and assessments by Poet et al. (2016), EPA (2015), and OECD (2007). All three of these sources determined that reproductive effects were the critical toxic effects of NMP, and they focused their risk assessments on reproductive toxicity. An EPA (IRIS or Superfund PPRTV) RfC or RfD is not available for NMP. An ATSDR Toxicological Profile and MRLs are not available for NMP. Texas (TCEQ) Effects Screening Levels are not available for NMP. California (CalOEHHA) does not have inhalation reference values for NMP, but does list it as a developmental toxicant for Proposition 65, with Maximum Allowable Dose Levels (MADLs) of 3200 ug/day (inhalation) and 17000 ug/day (dermal). Occupational Exposure Limits (OELs) are not available from NIOSH or ACGIH, however the American Industrial Hygiene Association (AIHA, 2013) has a Workplace Environmental Exposure Level (WEEL) of 10 ppm (40 mg/m^3, with a skin notation; no further documentation available). Roberts (2017, personal communication) reports that the Occupational Alliance for Risk Science (OARS) has conducted a re-evaluation of the WEEL and intends to propose an updated WEEL value of 15 ppm (60 mg/m^3) later in 2017.

Poet et al. (2016) evaluated several rat reproduction bioassays utilizing oral, inhalation, or dermal exposure to NMP. Poet et al. (2016) derived short-term and chronic OEL values for NMP using an updated physiologically based pharmacokinetic (PBPK) model, along with benchmark dose modeling. They focused on two developmental endpoints for human health risk assessment: increased incidence of skeletal malformations for acute exposures, and changes to fetal/pup body weight for repeated exposures to NMP. A PBPK model for NMP in humans was used to calculate human equivalent

concentrations corresponding to the internal dose point of departure (POD) values. Application of a total UF of 20-21 to the POD values yielded short-term and chronic OEL values of 86 and 24 ppm, respectively. These are equivalent to 344 and 96 mg/m^3, respectively, applying a conversion factor of: 1 ppm = 4 mg/m^3 for NMP (derived from the MW = 99.13 (EPA, 2015)). Because the dose-response data were assessed in terms of internal dose, data for routes other than inhalation (oral and dermal) were used to support the OEL derivation. A 5% increase of risk and its 95% lower confidence limit (BMDL05) was used in BMD modeling. For acute OEL derivation, a UF_T = 20 was utilized, consisting of UF_H = 6.3 ($UF_{H\text{-}tk}$ = 2 for toxicokinetic differences X $UF_{H\text{-}td}$ = 3.16 for toxicodynamic differences) for a healthy worker population, and $UF_{A\text{-}td}$ = 3.16 for toxicodynamic differences since the PBPK model was used for interspecies extrapolation and accounted for toxicodynamic differences. For skeletal malformation and the acute OEL derivation (with a UF_T = 20), acute OELs were 120 ppm for inhalation alone and 86 ppm for inhalation and dermal vapor exposures combined; preference was given to the lower value of 86 ppm. For the chronic OEL, also for a healthy worker population, a UF_T = 21 was used, consisting of the same UFs as described above except that $UF_{H\text{-}tk}$ was 2.1 rather than 2. This resulted in chronic OELs of 30 ppm for inhalation alone and 24 ppm for inhalation and dermal vapor exposures combined. The authors concluded that, “These OEL values are expected to be protective of the developmental effects of NMP observed in rats. In addition, these exposures are not expected to be associated with potential irritation in workers. Bader et al. (2006) reported that exposures to concentrations of 20 ppm (and peak exposures to 40 ppm) did not result in irritation, as indicated by a lack of exposure-related changes in eye blink rates, and breathing rates in human volunteers.” (Poet et al, 2016). It should be again noted that these proposed OELs were derived for healthy adult workers.

OECD (2007) reported that NMP is not irritating to the eyes and upper respiratory tract in humans, but is a skin irritant. They noted that, via the oral route in animal bioassays, NMP caused embryotoxicity and malformations in rats and rabbits which was not secondary to maternal toxicity. They regarded NMP as a low priority for further study, possessing a low hazard for human health.

EPA (2015) performed a toxicology literature review for a TSCA chemical risk assessment for paint stripper use. The assessment team included two EPA staff who co-authored the paper by Poet et al. (2016). The risk assessment was based on developmental toxicity associated with consideration of acute and repeated exposures. “Other hazards, in particular reproductive and other systemic effects, could be a concern at higher exposure levels, but exposures that are protective of pregnant women and women who may become pregnant are expected to also be protective of other lifestages and subpopulations.” (EPA, 2015). They used a PBPK model to calculate internal doses of NMP, based on a published, peer-reviewed model that was adapted and validated for use by EPA/OPPT. The risk assessment approach utilized a Margin of Exposure (MOE), and a MOE of 30 was selected; MOEs below 30 indicated the presence of risks (MOE = noncancer POD / human exposure estimate). Inter-individual variability was assumed, but was not quantified. This variability was reflected in the selection of uncertainty factors used in the selection of the MOE and the calculation of risk estimates, specifically 10X for intra-human variability and 3X for interspecies (extrapolation of rat to human) uncertainty.

EPA (2015) found that, “Nearly every study that evaluated developmental toxicity identified some type of adverse effect. Moreover, a review of effect levels reveals that the effects are observed with a comparable dose range, with NOAELs typically 100-200 mg/kg bw/day for oral exposure studies and effect levels ranging 479-612 mg/m^3 in the inhalation exposure studies. Specifically, EPA/OPPT identified a number of biologically relevant, consistent and sensitive effects that represent a continuum of reproductive and developmental effects, including decreased fetal and pup body weight, delayed ossification, skeletal malformations and increased fetal and pup mortality, for consideration in assessing human health risks.” (EPA, 2015). EPA (2015) selected decreased fetal body weights as a key endpoint for use in the risk calculation for chronic exposure. They noted that statistically significant increases in resorptions or mortality were seen consistently at administered doses of 500 – 1000 mg/kg bw/day in all studies at the tested doses; they selected fetal resorptions/fetal mortality as a key endpoint for the calculation of risks associated with acute exposures. Overall, they reported that, “The observed effects, even those from different studies, occur within a narrow range of doses of 100 to 1000 mg/kg bw/day (for oral exposures) or 470 to 669 mg/m^3 (for inhalation exposures).” They found that the repeated-dose NOAELs and LOAELs are 2 to 4-fold lower than single-dose values, showing these endpoints are more sensitive to repeated exposures; therefore, they concluded that fetal body weight reduction is most applicable to estimating risks for chronic exposures.

Fetal resorptions and fetal mortality was considered relevant to single exposures and was selected as the basis of the dose-response analysis for acute exposures (EPA, 2015). The acute effects were assumed to depend on exceedance of a threshold value for even a single day (i.e., peak concentrations) rather than a time-weighted average value. EPA/OPPT selected the combined analysis of the Saillenfait et al. (2002) oral study and the Saillenfait et al. (2003) inhalation study for the derivation of the POD, 216 mg/l (internal dose); using the dose metric of C_{max} this POD had an equivalent administered dose (using PBPK) of 218 mg/kg bw/day (oral) and using the dose metric of Area Under the Curve (AUC) this POD had an equivalent administered dose (using PBPK) of **217 mg/kg bw/day (oral)** (see table 3-4 of EPA (2015)).

For the assessment of repeated exposures, decreased fetal body weight was selected as the endpoint of concern, and the study of Saillenfait et al. (2003) was selected for the POD with an internal dose (AUC) equivalent to an applied oral dose (via PBPK) of **48 mg/kg bw/day** (see Table 3-5 of EPA (2015)). While the POD for the DuPont (1990) study was lower than the Saillenfait et al. (2003) study, the dose-response relationship in the DuPont study was not as robust and was therefore not selected (EPA, 2015).

EPA (2015) provided further discussion of the selection of UFs in Table 4-2. Specifically, $UF_A = 3$ was selected; $UF_{A\text{-}td} = 3$ for toxicodynamic differences, and toxicokinetic differences between laboratory animals and humans were accounted for by the use of PBPK modeling. $UF_H = 10$ accounts for the variation in sensitivity within the human population (human variability); the PBPK modeling did not account for human pharmacokinetic variability. It is noted that the $UF_T = 30$ of EPA (2015) is somewhat larger than those of Poet et al. (2016) ($UF_T = 20$ or 21); the former derived benchmarks for the protection of the general population who may be exposed via

household product use, while the latter derived proposed WEELs for the protection of healthy adult workers.

For the calculation of candidate ITSLs, the dose-response and risk estimation methods of EPA (2015) may be utilized as follows, applying the oral-to-inhalation route conversion factors of Rule 232(1)(b) to the applied oral doses of EPA (2015):

Potential ITSL #1 for protection from increased fetal resorptions with a single peak inhalation exposure (based on the EPA (2015) POD equivalent dose, acute exposure for a consumer and a single paint stripping project, or occupational exposure for a single 8 hr workday; see p. 82 and Table 4-2 of EPA (2015)):

Potential ITSL = $\frac{217 \text{ mg/kg bw/day}}{UF_T = 30} \times \frac{70 \text{ kg}}{20 \text{ m}^3/\text{d}} \times \frac{1000 \text{ ug}}{\text{mg}} = 25{,}317 \text{ ug/m}^3$

= ~ 25,000 ug/m^3 (= 6.3 ppm) (8 hr AT)

It is noted that this value is more restrictive than the proposed OEL of 15 ppm (Poet et al, 2016), perhaps largely due to the somewhat larger UF_T employed by EPA (2015) in addition to modifications/updates in the modeling by Poet et al. (2016). This value is similar to, but somewhat more restrictive than, the current WEEL of 10 ppm for the protection of healthy adult workers (AIHA, 2013).

Potential ITSL #2 for protection from decreased fetal body weight with repeated daily exposures via ambient air (based on the EPA (2015) POD equivalent dose, occupational use and repeated workday exposures):

Potential ITSL = $\frac{48 \text{ mg/kg bw/day}}{UF_T = 30} \times \frac{70 \text{ kg}}{20 \text{ m}^3/\text{d}} \times \frac{1000 \text{ ug}}{\text{mg}} = 5{,}600 \text{ ug/m}^3$

= 5,600 ug/m^3 (= 1.4 ppm) (24 hr AT) (a 24 hr averaging time is appropriate, given that the critical effect is reproductive toxicity associated with repeated exposures during pregnancy, and given that an ITSL may be applied to repeated daily ambient air impacts and exposures).

The ITSL is 5,600 ug/m^3 (24 hr AT), consistent with Potential ITSL #2 above. This value is selected because it appears to be more restrictive than Potential ITSL #1 above, and therefore it should ensure protection from developmental toxicity with peak exposures of shorter duration than 24 hours as well as repeated daily exposures during the window of vulnerability of gestation.

References:

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