Choice of Critical Study

- OEHHA determined Staples (1990) to be the critical study because:
  - "... *the Staples study design goes beyond what is required by the guidelines ... (e)xposure of both parents and a longer gestational exposure ... might be anticipated to cause effects not detectable in the shorter study.*" (OEHHA; June, 2009)
- Producers Group believes Saillenfait *et al.* (2003) is the key study because:
  - Saillenfait protocol uses larger group sizes.
  - Current reproduction and developmental study protocols require the induction of parental toxicity. The older Staples protocol did not induce maternal toxicity.
  - Choice of Saillenfait, not Staples, is consistent with (a) OEHHA guidance requiring selection of the valid study with the highest NOAEL among studies for the critical endpoint, and (b) the judgement of the International regulatory community (OECD, 2007).
  - Premating and early gestation exposures used by Staples do not affect fetal / pup BW:
    - Pre-mating exposures not required for steady-state NMP blood levels during gestation.
    - Oral pre-mating exposures of both parents did not enhance toxicity seen with shorter, dam-only oral exposures - in guideline reproduction and developmental studies, BW decrements occur at the same parental / maternal NMP blood levels (Table 6; Poet et al., 2009)
    - Oral pre-mating exposures (100 mg/kg) of paternal rats to 100 mg/kg NMP did not affect pup BW (Sitarek and Stetkiewicz, 2008), even though NMP blood levels are 5-fold higher than can be achieved via inhalation of saturated NMP vapor (Table 6; Poet et al., 2009)

Uncertainty Factor (UF)

- OEHHA recommends a combined UF of 60
  - 6-fold for an interspecies UF (OEHHA, 2008)
  - 10-fold for an intraspecies UF
- Producers Group believes the OEHHA recommendation is unduly conservative
  - OEHHA (2008) recommends an interspecies UF 3. An UF of 6 is recommended when a compound- and species-specific pharmacokinetic model is unavailable. An NMP PBPK model for rats exists and was judged reasonable by OEHHA.
  - PBPK model could be used in future effort to derive a chemical-specific adjustment factor that would lower the 10-fold intraspecies UF .

Physiologically Based Pharmacokinetic (PBPK) Model for NMP

- OEHHA concludes the rat PBPK model:
  - Is reasonable - agree
  - Has some uncertainty due to omission of pre-mating exposure – disagree
  - Provide no benefit over use of external air concentrations – disagree
- OEHHA concludes the human PBPK model is not ready for RA use:
  - Underestimates human blood data in Xiaofei et al. (2000) – disagree
  - Has uncertainty regarding [maternal blood] and [fetal tissue] of NMP – agree, but model assumes worst-case
  - Lacks sensitivity analysis for cardiac output and alveolar ventilation – analysis available
- Producer Group notes that the human database is more extensive than that of the rat – OEHHA rationale does not support exclusion of human PBPK model

Benchmark Response (BMR)

- OEHHA concludes 5% BMR is biologically meaningful - disagree
  - 5% BMR most conservative of BMRs historically used by USEPA (5%, 10%, 1 SD)
  - USEPA use of 5% BMR overstated – not used for MIBK
  - *"In the case of pup or fetal body weight, there is no specific decrement generally regarded as indicative of an adverse effect."* (IRIS RfD for MEK; USEPA, 2003)
- Producers Group conservatively uses 1 SD (6%) BMR for Saillenfait *et al.* (2003)
  - 1 SD BMR more commonly used by USEPA than 5% BMR (Sapphire, 2009)
  - I SD or 10% are only BMRs used for USEPA for RfC determinations (Sapphire, 2009)
  - Fetal / pup decrements caused by NMP – an irritant – occur only at saturated vapor concentrations and are probably not biologically meaningful in the real- / experimental-world
    - Pup BW decrement (11%) reported by Staples (1990) at LOAEL was transient – BW returned to control levels one week after weaning and exposed pups reproduced normally.
    - BW decrements seen at vapor saturation may be multi-factorial (e.g., sensory irritation) - BW decrements via other routes require **4-** to 7-fold higher blood levels (Table 6; Poet et al., 2009).
    - Exposures to current NMP OELs (10 - 20 ppm) are not irritating (van Thriel et al., 2007)