NMP Background

- Rich toxicological and PK database in rodents + humans:
  - Transient fetal / pup BW decrease – most sensitive effect
  - Parent compound responsible for effect
  - NMP ADME in rats and humans comparable
- Internationally recognized OEL = 10 ppm (SCOEL, 2007)
- CA / Producer Group PEL analyses:

NMP PEL (UF) in ppm

METHOD	HESIS (2006)	OEHHA (2007)	HEAC	Producer Group
NOEC	5 (10)	2 - 5 (10-30)	1 (30)	---
BMD	---	---	1 (60)	8 (10)
PBPK	---	---	TBD	10 (10-30)

- Differences between CA / Producer Group PELs due to:
  - Choice of key study: Saillenfait et al., 2003 vs Staples, 1990
  - Methodology: EPA default vs OEHHA policy
  - Choice of UFs

Methodological Overview

REL Development Process*

conduct literature search

⇓

choose best study, emphasizing human data

⇓

identify critical biological endpoint

⇓

estimate threshold for effect (benchmark or NOAEL)

⇓

temporal/dosimetric adjustments (time extrapolation, HEC, Children's HEC, PBPK)

⇓

account for uncertainties in data (extrapolating animal data to humans; occupational studies to sensitive subgroups)

⇓

Reference Exposure Level (REL)
(listed in Appendix B & Appendix D)

OECD (2007) / HEAC (2009)

⇓

Saillenfait et al. (2003) / Staples (1990)

⇓

Reduced rat fetal / pup body weight

⇓

Benchmark (BMD/BMC)

⇓

PBPK HEC Derivation

⇓

HEAC (TBD) / Industry (10 - 30)

* Technical Support Document for the Derivation of Noncancer Reference Exposure Levels (OEHHA, 2008)

Preferred PEL Approaches (*OEHHA, 2008*)

PBPK Model: *If sufficient data are available, PBPK modeling will be used to determine the tissue dose in a default human model if an animal toxicity study is used. The relationship determined by the PBPK model will replace the pharmacokinetic portion (UF^{A-k}) of the interspecies uncertainty factor (UF^{A}).*

- Assesses species-specific target tissue doses via realistic physiological / biochemical parameters
- Allows extrapolation to simulated pregnancy conditions
- Use to adjust for the time and duration of exposure from multiple routes

BMC Analysis: … *the BMC approach is preferred. Quantal or continuous dose-response data for a toxicant (measured for at least two dose levels and a control) are required …..*

- Useful for studies with a graded dose-response
- BMD analysis useful for studies that show graded responses, extrapolation from this point of departure to a health protective level for the target human population is by means of explicit models
- Applied to **internal dose**, using PBPK model

HEC: Rat exposures for studies of interest simulated using PBPK model to determine the AUC for NMP in maternal blood. That AUC used to determine the rat internal BMCL. Human PBPK model is then used to back-calculate from the internal BMCL to an external concentration in a human that would lead to the same AUC

	[External]		Internal Dose	[External]
Study	@ NOEL	@ LOEL	@ BMCL	@ BMCL
Saillenfait et al. (2003)	60 ppm	120 ppm	340 (mg·hr/L)	102 ppm
Staples (1990)	51 ppm	116 ppm	360 (mg·hr/L)	107 ppm

Summary

- A PBPK model for NMP has been developed and calibrated against rat and human data
- Model-derived HEC based on internal dose metric in rats

	Internal Dose (BMCL)	External Concentration
Rat	350 (mg·hr/L)	105 (ppm 6 hr/d/GD)
Human	350 (mg·hr/L)	480 (ppm, 8 hr/d, 5 d/wk) *

- HEC (480 ppm) ÷ combined UF (10 - 30) = NMP PEL consistent with current OELs of 10 – 20 ppm (SCOEL, AIHA, MAK)
- UF considerations:
  - 1 (UF_{A-k}) × 2 or √10 (UF_{A-d}) × √10 (UF_{H-k}) × √10 (UF_{H-d}) = 20 - 30 (Table 4.4.1; OEHHA, 2008)
  - Decades of safe use internationally under IH monitoring
  - Recommendation for biomonitoring

*workplace exposure via both the inhalation and dermal absorption of NMP vapor