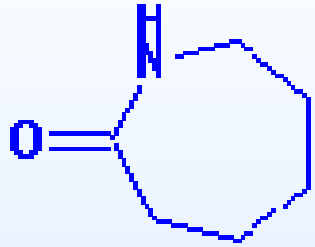
Caprolactam
Reference Exposure Levels

Scientific Review Panel Meeting

January 21, 2011

Office of Environmental Health Hazard Assessment

Caprolactam
Uses and Sources



- **Used to manufacture fibers and resins (Nylon 6)**
- **Potentially emitted from facilities that manufacture, use, or recycle Nylon 6**
- **Found in carpeting and furniture products**

What Are Reference Exposure Levels?

- **Cal/EPA uses Reference Exposure Levels (RELs) in risk assessments of airborne chemicals**
- **RELs are concentrations in air at or below which no adverse health impacts are anticipated following exposure for specified periods.**

  Assumes threshold for effects

- **They are meant to protect most people, including sensitive individuals.**

- **Exceeding the REL does not necessarily result in adverse health consequences.**

REL Development

- **Literature search**
- **Identify critical endpoints and studies**
- **Identify Point of Departure (POD)**

  NOAEL - No Observed Adverse Effect Level

  LOAEL - Lowest Observed Adverse Effect Level

  Benchmark concentration (BMC)
- **Apply any necessary time or dosimetric adjustments and uncertainty factors**

REL Development (contd)

$$\text{REL} = \frac{(\text{POD})\ (\text{dose ADJ})\ (\text{time ADJ})}{\text{Uncertainty Factors}}$$

For inhalation exposure, the POD will be an airborne concentration

Units usually either ppm or $\mu g/m^3$

Benchmark Dose (Concentration)

- **A BMD (or BMC) is a dose (or concentration) that causes a specific level of effect (e.g., 5% response) derived from curve fitting of dose response data.**
- **Incorporates slope, dose-response curve, and sample size information.**
- **Unlike NOAEL, BMD is not directly dependent on choice of exposure level by investigator.**
- **USEPA has developed a computer program to calculate the benchmark concentration, available on-line at: http://www.epa.gov/NCEA/bmds/index.html**

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Reference Exposure Levels (RELs)

Proposed RELs

- **Acute (1 Hour): 770 µg/m^3 (170 ppb)**
- **8 Hour: 7 µg/m^3 (1 ppb)**
- **Chronic: 2 µg/m^3 (0.5 ppb)**
- **RELs are based on irritation and/or injury to upper airways**

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Worker Exposure Studies

- **Upper respiratory tract irritation, eye irritation, dermal contact irritation**
- **Acute irritant at 10 ppm (46 mg/m^3), but no clear dose-response data for NOAEL**
- **No robust data on long-term exposure in humans**

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Acute REL Derivation

- Based on an occupational study by Ferguson & Wheeler (1973) in unacclimated workers
- Five workers stood various distances from emission source of caprolactam vapor for several minutes
- Exposures were 10, 14, 25 and 104 ppm (46, 65, 116 and 482 mg/m^3)
- Most or all workers experienced transient nasal irritation at all concentrations

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Acute REL Derivation Cont.

- **LOAEL of 10 ppm (46 mg/m^3) and above led to transient nasal and throat irritation**
- **No time adjustment – Conc. dependent**
- **Applied LOAEL-to-NOAEL UF = 6**
- **Intraspecies UFs:**
  - **toxicokinetic $UF_{H\text{-}k}$ = 1 (site of contact irritant)**
  - **toxicodynamic $UF_{H\text{-}d}$ = 10 (for human variation)**
- **Cumulative UF = 60**
- **Acute REL = 770 µg/m^3 (170 ppb)**

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8 Hour & Chronic REL Derivation

- **Based on 13-week rat study,**

  5 days/wk, 6 hrs/day at 24, 70, and 243 mg/m^3 (Reinhold et al., 1998)

- **Treatment-related increase in labored breathing, nasal discharge, nasal and laryngeal tissue damage**

- **No NOAEL; LOAEL = 24 mg/m^3**

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8 Hour & Chronic REL Derivation Cont.

- **BMC approach: $BMCL_{05}$ = 3 mg/m^3**
  (dose-dependent nasal/larynx tissue injury)
- **Time adjustment:**
  8 Hour = 1.607 mg/m^3 (3*6/8*5/7)
  Chronic = 0.536 mg/m^3 (3*6/24*5/7)
- **Human equivalent concentration (US EPA), based on regional gas dose ratio (0.25):**
  8 Hour = 0.402 mg/m^3
  Chronic = 0.134 mg/m^3

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Benchmark Concentration

Dose-response data for nasalturbinal and laryngeal lesions

Endpoint	Exposure Group (mg/m^3)			
	0	24	70	243
Nasal respiratory mucosa	0/20	4/20	9/20	12/20
Nasal olfactory mucosa	0/20	2/20	8/20	17/20
Laryngeal tissue	0/20	5/20	12/20	20/20

Pathologist grading table modifications:

- Moderate changes only for respiratory mucosa
- Slight, moderate and moderately severe for olfactory mucosa

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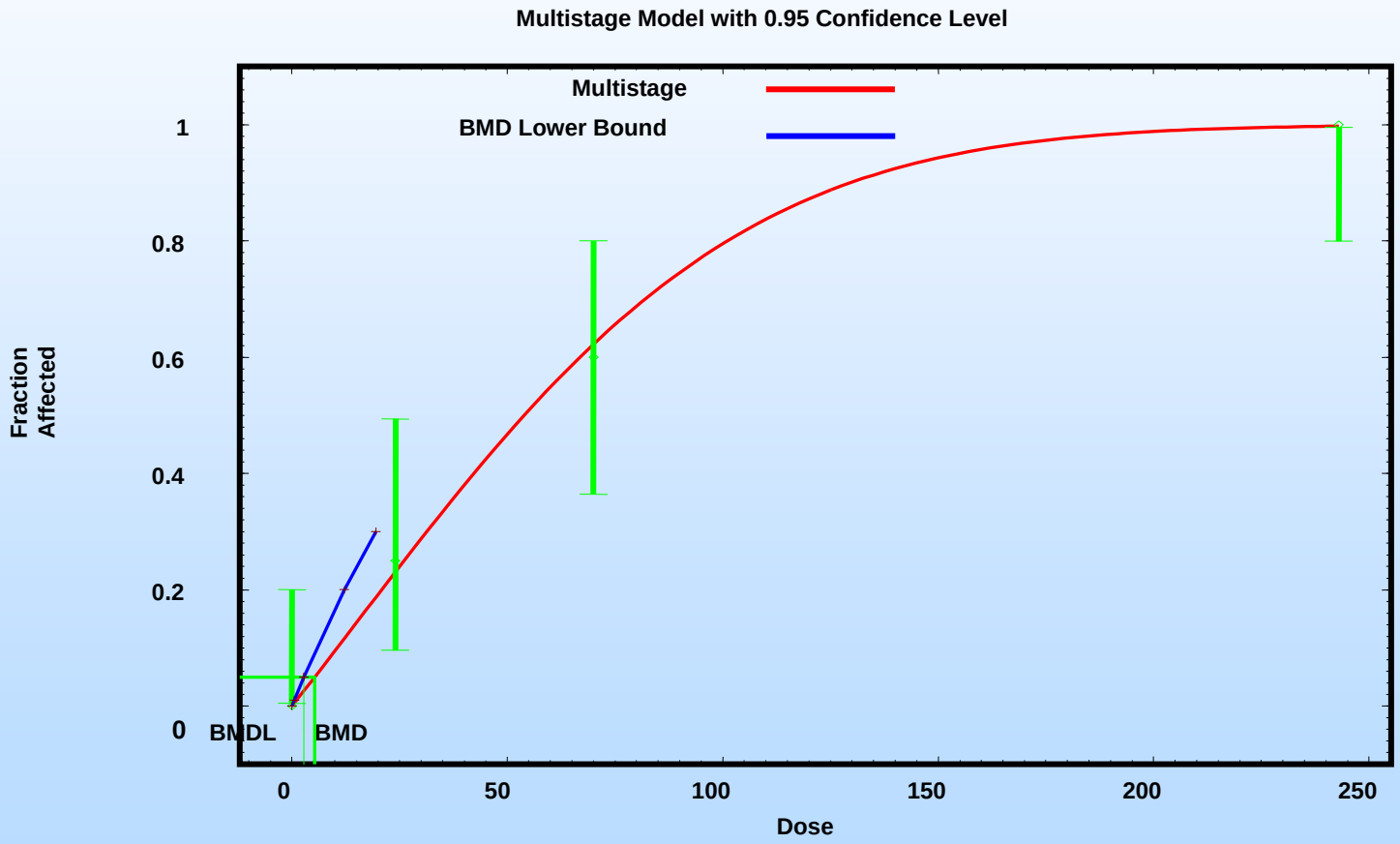
Benchmark Concentration

Endpoint	$BMCL_{05}$ (model)	BMC_{05} (mg/m^3)	*P* Value	AIC
Nasal respiratory mucosa changes	4 mg/m^3 (log-logistic)	6.4	0.88	76.52
Nasal olfactory mucosa changes	12 mg/m^3 (log-probit)	17	0.99	60.85
Laryngeal tissue changes	3 mg/m^3 (multistage)	5.3	0.94	53.59

- **$BMCL_{05}$** - 95% lower confidence interval at the 5% response rate (BMC_{05})

Reinhold et al. (1998) data for subchronic caprolactam exposure; laryngeal tissue changes at sacrifice in rats.



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8 Hour & Chronic REL Derivation Cont.

Uncertainty Factor application:

- Subchronic UF = 2 (13 weeks considered borderline chronic exposure for rodents; evidence indicates UF = 2 or less)
- Interspecies UFs:
  - toxicokinetic $UF_{A\text{-}k}$ = 1 (RGDR applied, direct-acting irritant)
  - toxicodynamic $UF_{A\text{-}d}$ = $\sqrt{10}$ (lack of data)

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8 Hour & Chronic REL Derivation Cont.

Uncertainty factors (continued):

- **Intraspecies UFs:**
  - **toxicokinetic UF_{H-k} = 1 (site of contact irritant)**
  - **toxicodynamic UF_{H-d} = 10 (for human variation)**
- **Cumulative UF = 60**
- **<u>8-Hour REL</u>: 7 µg/m³ (1 ppb)**
- **<u>Chronic REL</u>: 2 µg/m³ (0.5 ppb)**

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Reproduction/Developmental Studies

- **Only oral animal repro/dev exposure studies**
- **Fetotoxicity (reduced fetal body weight)**

  NOAEL 700 mg/kg; LOAEL 3500 mg/kg
- **Route-to-route extrapolation (oral-to-inhalation) + 100-fold UF: 24 mg/m^3**
- **RELs based on upon airway irritancy will be protective for repro/dev effects**

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Summary

- **Proposed RELs:**
  - **Acute: 770 µg/m^3 (170 ppb)**
  - **8 Hour: 7 µg/m^3 (1 ppb)**
  - **Chronic: 2 µg/m^3 (0.5 ppb)**

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Reference Exposure Levels

Response to Public Comments

Occupational & human exposure studies ignored for 8 hour and chronic REL development

- Occupational studies not adequate for chronic effects (exposure duration, concentration, description of chronic injury not well documented, target upper airway region not investigated)
- Acute human exposure study (Zeigler et al., 2008) cannot be used to derive a chronic REL

POD of 5 mg/m^3 for acute REL based on Zeigler et al. (2008) should be used

- Free-standing NOAEL for sensory irritation (5 mg/m^3) not ideal for REL derivation
- Increased total symptom score (at 5 mg/m^3), likely odor-driven (a NOEL rather than a NOAEL)
- Alternative study used instead

8 Hour and chronic RELs orders of magnitude below other standards (e.g., ACGIH TLV)

- **ACGIH TLV (5 ppm, 23 mg/m^3) based on essentially acute effects of acclimated workers (Ferguson & Wheeler study), not designed to protect general population (i.e., infants, elderly, infirm)**
- **European LCI (240 µg/m^3) POD based on free-standing NOAEL for systemic effects in rat study (243 mg/m^3)**

Upper airway changes in rat study are “adaptive” vehicle-related, not true adverse effects

- **Aerosolized aqueous caprolactam solution**
- **Upper airway lesions considered critical endpts by OEHHA :**

  Goblet cell hypertrophy & hyperplasia (resp. epith.)

  Eosinophilic material (olfac. epith.)

  Squamous metaplasia (larynx)


Office of Environmental Health Hazard Assessment
OEHHA
State of California

DEFAULT UNCERTAINTY FACTORS used in CA Air Program - ACUTE, 8-HOUR AND CHRONIC RELS

Factor	Values Used		REL types
LOAEL uncertainty factor (UF_L)			
Values used:	1	NOAEL or benchmark used	A, 8, C
	6	LOAEL, mild effect	A
	10	LOAEL, severe effect	A
	10	LOAEL, any effect	8, C

DEFAULT UNCERTAINTY FACTORS used in CA Air Program - ACUTE, 8-hR AND CHRONIC RELS

Factor	*Values Used*	*REL types*
Subchronic uncertainty factor (UF_{subch})		
Values used:	3 if evidence no additional toxicity would occur with longer-term exposure	C
	10 Typically used	

DEFAULT UFs used in CA Air Program - Interspecies

Factor	*Values Used*	*REL types*
Interspecies ($UF_{A\text{-}k}$) *Toxicokinetic component*	1 PBPK models describe differences 2 residual toxicokinetic differences; non-primate; HEC or incomplete DAF √10 non-primate studies with no chemical- or sp.-specific kinetic data	A, 8, C
Interspecies ($UF_{A\text{-}d}$) *Toxicodynamic component*	1 mechanistic data fully describe differences. 2 for residual susceptibility differences given some toxicodynamic data √10 non-primate studies with no data on toxicodynamic interspecies differences	A, 8, C

DEFAULT UFs used in CA Air Program - Intraspecies Acute, 8-hr and Chronic RELS

Factor	*Values Used*	*REL types*
Intraspecies (UF_{H-k}) *Toxicokinetic component*	1 Study used sensitive subpopulations (e.g., infants and children)	A, 8, C
	1 PBPK model including measured inter-individual variability is used.	
	√10 for residual susceptibility differences; some toxicokinetic data (e.g., PBPK for adults only)	
	10 to allow for diversity, including infants and children, with no human kinetic data	

DEFAULT UFs used in CA Air Program - Intraspecies Acute, 8-hour and Chronic RELS

Factor	*Values Used*	*REL types*
Intraspecies ***(UFH-d)*** *Toxicodynamic component*	1 Human study including sensitive groups (e.g., infants and children) √10 Studies of normal adult subjects only, but no suspicion additional susceptibility of children 10 Suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)	A, 8, C