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)

REL = (POD) (dose ADJ) (time ADJ)

Uncertainty Factors

For inhalation exposure, the POD will be an airborne concentration
Units usually either ppm or µg/m³
**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
Caprolactam
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
Caprolactam
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/m³)

- Most or all workers experienced transient nasal irritation at all concentrations
Caprolactam
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 UF:
  - toxicokinetic UF_{H-k} = 1 (site of contact irritant)
  - toxicodynamic UF_{H-d} = 10 (for human variation)
- Cumulative UF = 60
- Acute REL = 770 µg/m^3 (170 ppb)
Caprolactam
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$^3$
Caprolactam
8 Hour & Chronic REL Derivation Cont.

- BMC approach: $BMCL_{05} = 3 \text{ mg/m}^3$
  (dose-dependent nasal/larynx tissue injury)

- Time adjustment:
  8 Hour = $1.607 \text{ mg/m}^3 (3\times 6/8 \times 5/7)$
  Chronic = $0.536 \text{ mg/m}^3 (3\times 6/24 \times 5/7)$

- Human equivalent concentration (US EPA), based on regional gas dose ratio (0.25):
  8 Hour = $0.402 \text{ mg/m}^3$
  Chronic = $0.134 \text{ mg/m}^3$
Caprolactam

Benchmark Concentration

Dose-response data for nasalturbinal and laryngeal lesions

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Exposure Group (mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Nasal respiratory mucosa</td>
<td>0/20</td>
</tr>
<tr>
<td>Nasal olfactory mucosa</td>
<td>0/20</td>
</tr>
<tr>
<td>Laryngeal tissue</td>
<td>0/20</td>
</tr>
</tbody>
</table>

Pathologist grading table modifications:
- Moderate changes only for respiratory mucosa
- Slight, moderate and moderately severe for olfactory mucosa
# Caprolactam Benchmark Concentration

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>BMCL&lt;sub&gt;05&lt;/sub&gt; (model)</th>
<th>BMC&lt;sub&gt;05&lt;/sub&gt; (mg/m&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>P Value</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal respiratory mucosa changes</td>
<td>4 mg/m&lt;sup&gt;3&lt;/sup&gt; (log-logistic)</td>
<td>6.4</td>
<td>0.88</td>
<td>76.52</td>
</tr>
<tr>
<td>Nasal olfactory mucosa changes</td>
<td>12 mg/m&lt;sup&gt;3&lt;/sup&gt; (log-probit)</td>
<td>17</td>
<td>0.99</td>
<td>60.85</td>
</tr>
<tr>
<td>Laryngeal tissue changes</td>
<td>3 mg/m&lt;sup&gt;3&lt;/sup&gt; (multistage)</td>
<td>5.3</td>
<td>0.94</td>
<td>53.59</td>
</tr>
</tbody>
</table>

- **BMCL<sub>05</sub>** - 95% lower confidence interval at the 5% response rate (BMC<sub>05</sub>)
Reinhold et al. (1998) data for subchronic caprolactam exposure; laryngeal tissue changes at sacrifice in rats.
Uncertainty Factor application:

- **Subchronic UF = 2** (13 weeks considered borderline chronic exposure for rodents; evidence indicates UF = 2 or less)

- **Interspecies UF**s:
  - **toxicokinetic** $A_k = 1$ (RGDR applied, direct-acting irritant)
  - **toxicodynamic** $A_d = \sqrt{10}$ (lack of data)
Uncertainty factors (continued):

- Intraspecies UF s:
  - toxicokinetic $U_{H-k} = 1$ (site of contact irritant)
  - toxicodynamic $U_{H-d} = 10$ (for human variation)

- Cumulative UF = 60

- 8-Hour REL: 7 µg/m$^3$ (1 ppb)
- Chronic REL: 2 µg/m$^3$ (0.5 ppb)
Caprolactam
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/m³

- RELs based on upper airway irritancy will be protective for repro/dev effects
Caprolactam
Summary

- Proposed RELs:
  - Acute: 770 µg/m³ (170 ppb)
  - 8 Hour: 7 µg/m³ (1 ppb)
  - Chronic: 2 µg/m³ (0.5 ppb)
Caprolactam 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)
DEFAULT UNCERTAINTY FACTORS used in CA Air Program - ACUTE, 8-HOUR AND CHRONIC RELS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Values Used</th>
<th>REL types</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOAEL uncertainty factor ($UF_L$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Values used:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1  NOAEL or benchmark used</td>
<td>A, 8, C</td>
<td></td>
</tr>
<tr>
<td>6  LOAEL, mild effect</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>10 LOAEL, severe effect</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>10 LOAEL, any effect</td>
<td>8, C</td>
<td></td>
</tr>
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### DEFAULT UNCERTAINTY FACTORS used in CA Air Program - ACUTE, 8-hR AND CHRONIC RELS

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<tr>
<td><strong>Subchronic uncertainty factor</strong> ( (UF_{subch}) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Values used:</strong></td>
<td>3 if evidence no additional toxicity would occur with longer-term exposure</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>10 Typically used</td>
<td></td>
</tr>
</tbody>
</table>
# DEFAULT UF$\text{S used in CA Air Program - Interspecies}$

<table>
<thead>
<tr>
<th>Factor</th>
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<th>REL types</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interspecies</strong> ($U_{A-k}$)</td>
<td>1    PBPK models describe differences</td>
<td>A, 8, C</td>
</tr>
<tr>
<td>Toxicokinetic component</td>
<td>2    residual toxicokinetic differences; non-primate; HEC or incomplete DAF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>√10  non-primate studies with no chemical- or sp.-specific kinetic data</td>
<td></td>
</tr>
<tr>
<td><strong>Interspecies</strong> ($U_{A-d}$)</td>
<td>1    mechanistic data fully describe differences.</td>
<td>A, 8, C</td>
</tr>
<tr>
<td>Toxicodynamic component</td>
<td>2    for residual susceptibility differences given some toxicodynamic data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>√10  non-primate studies with no data on toxicodynamic interspecies differences</td>
<td></td>
</tr>
</tbody>
</table>

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

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<tr>
<th>Factor</th>
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<tr>
<td><strong>Intraspecies</strong> (UF&lt;sub&gt;H-k&lt;/sub&gt;)</td>
<td>Study used sensitive subpopulations (e.g., infants and children)</td>
<td>A, 8, C</td>
</tr>
<tr>
<td>Toxicokinetic component</td>
<td><strong>1</strong> PBPK model including measured inter-individual variability is used. √10 for residual susceptibility differences; some toxicokinetic data (e.g., PBPK for adults only)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 to allow for diversity, including infants and children, with no human kinetic data</td>
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<tr>
<td><strong>Intraspecies (UFH-d)</strong></td>
<td>1 Human study including sensitive groups (e.g., infants and children)</td>
<td>A, 8, C</td>
</tr>
<tr>
<td>Toxicodynamic component</td>
<td>√10 Studies of normal adult subjects only, but no suspicion additional susceptibility of children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 Suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)</td>
<td></td>
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