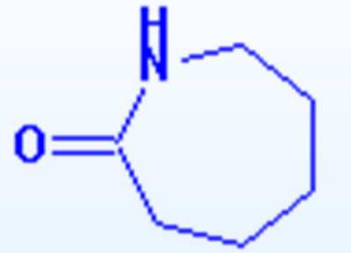
Caprolactam
Reference Exposure Levels

Scientific Review Panel Meeting

May 3, 2011

Office of Environmental Health Hazard Assessment

Caprolactam
Uses and Sources



- **Monomer used for manufacture of Nylon-6**
- **Production: 1 billion lbs or more in 2006**
- **75% of Nylon-6 used in fibers (carpet, rugs, clothing, etc.)**
- **Emissions: caprolactam production and manufacture, use, recycling of Nylon-6**

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Changes to the Document

- **Changed procedure for rounding REL values**
- **No recommendation for an acute REL**
- **Added:**
  - **detail to our review of some studies**
  - **section on occupational standards**
  - **summaries of additional studies to provide more complete picture**
  - **details on caprolactam aerosol/particle size and exposure implications**
  - **pathology findings and conclusions on upper respiratory irritant effects**

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Proposed Reference Exposure Levels (RELs)

- **Fix rounding problem with 8-hr/chronic RELs**

Rounding to 1 significant figure:

8 Hour: 7 µg/m^3 (Rounded up from 6.70 µg/m^3)
1 ppb (Rounded down from 1.446 ppb)

Chronic: 2 µg/m^3 (Rounded down from 2.23 µg/m^3)
0.5 ppb (Rounded up from 0.48 ppb)

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Proposed REL Value Adjustments

- **Proposed fix by Dr. Nazaroff:**

  Use 2 significant figures when 1st digit is "1" or "2" to reduce introduced error from rounding.

- **8 Hour: 7 µg/m³ (1.4 ppb) 5-fold**
- **Chronic: 2.2 µg/m³ (0.5 ppb) 4.4-fold**

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No Acute REL Recommendation

Occupational study limitations (Ferguson & Wheeler, 1973)

- **Most (4/5) workers experienced transient nasal irritation at 10 ppm (46 mg/m^3)**
  - **Only 5 participants per concentration**
  - **Exposed to uncontrolled emission source**
  - **Concentration said to vary during exposure, but not reported (unknown SD)**
  - **LOAEL only (no NOAEL)**
  - **Measurement method antiquated**

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Acute Study Limitations

Human Chamber study (Ziegler et al. 2008)

Exposure: 0, 0.15, 0.5, 5 mg/m^3 for 6 hours

Limitation: Only have free-standing NOAEL

Subjective measures

- 29 questions placed in 7 subgroups – **except for odor, no individual or subgroup changes**
  - Symptom questions not independent
  - Total symptom score elevated at 5 mg/m^3, but almost certainly odor driven

Objective measures

- **Non-significant trends** for eye blink, nasal resistance, and eye redness

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Friedman Test Applied to Ziegler Data

Ranks assigned to summary statistics:

Table 3. Rank order of response by dose among five outcome measures

Study Measure	Exposure Concentration (mg/m^3)			
	0	**0.15**	**0.5**	**5.0**
Blink frequency median	2	3	1	4
Redness at max time (360 min)	1.5	3	1.5	4
Nasal resistance	1	2	3	4
Eye sx score median	1	2	3.5	3.5
Nasal sx score median	1	2	3	4

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Friedman Test Applied to Ziegler Data

Findings:

- **Significant differences (p=0.02) in ranks by concentration found using medians**
- **Significant difference (p<0.01) using Page trend test using medians**

But, important limitation:

- **Friedman test normally applied to individual data; use of summary data ignores the distribution and variance**
- **Need raw data – if obtained, we will re-evaluate**

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8 Hour & Chronic REL Derivation

- **13-week rat study (Reinhold et al., 1998)**

  6 hrs/day, 5 days/wk, at 24, 70, and 243 mg/m^3

- **Observed treatment-related increase in labored breathing, nasal discharge during exposure**
- **Histopathology at sacrifice: treatment-related increase in nasal and laryngeal tissue lesions**
- **No NOAEL; LOAEL = 24 mg/m^3**

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Added Table with Pathologist Grades

Table 5. Summary of Significant Findings in Nasoturbinal and Laryngeal Tissues at Terminal Sacrifice, Males and Females Combined.

Tissue and Pathologist Grade[a]	Exposure Group (mg/m^3)			
	0	24	70	243
Nasal respiratory mucosa[b]				
No change	1	0	0	0
Minimal	5	7	2	0
Slight	14	9	9	8
Moderate	0	4	9	12
Nasal olfactory mucosa[c]				
No change	3	5	2	0
Minimal	17	13	10	3
Slight	0	2	6	3
Moderate	0	0	2	10
Moderatly severe	0	0	0	4
Laryngeal tissue[d]				
No change	20	15	8	0
Minimal	0	5	12	12
Slight	0	0	0	8

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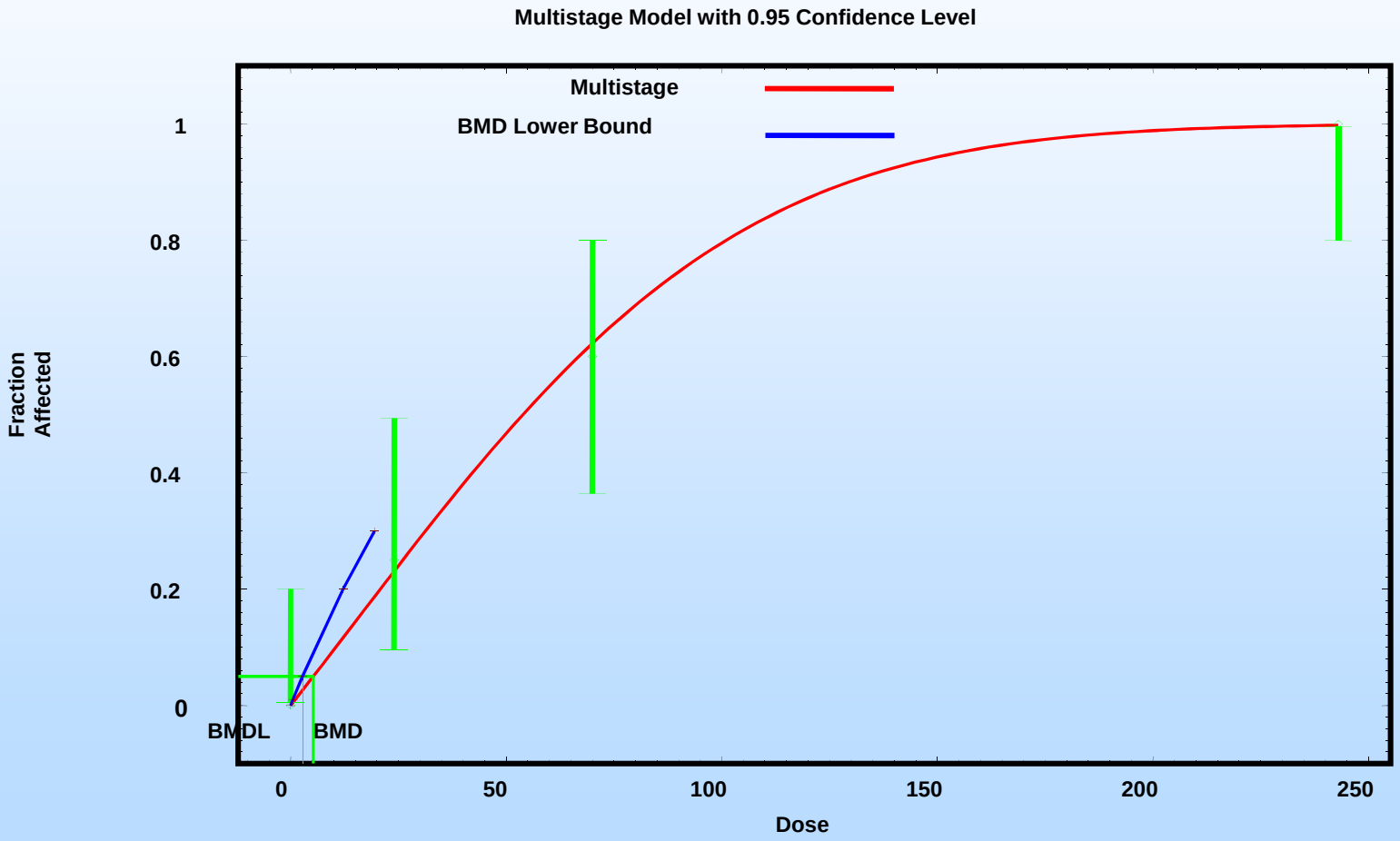
8 Hour & Chronic REL Derivation

- Incidence of treatment-related lesions after removal of background, age-related 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

- Dose-response for nasal and laryngeal lesions

Benchmark Concentration (BMC) for laryngeal lesions
POD = 3 mg/m³ (95% LCL at the 5% response rate)



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8-Hour and Chronic REL Summary

- **No REL derivation changes from previous draft**
- **POD is 3 mg/m^3**
- **After application of dose and time adjustments, and uncertainty factors, the proposed RELs are:**
  - **8 Hour: 7 µg/m^3 (1.4 ppb)**
  - **Chronic: 2.2 µg/m^3 (0.5 ppb)**

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Added Animal and Human Studies

- **Oral (in diet) 90-d study in dogs by Hazelton labs (1980)**
- **Tuma (1981) case report - grand mal seizures & dermal injury from 3-day high-level worker exposure**
- **Added section on human and animal dermal sensitization studies**

Material sent to Panel

- **The Panel members received additional material from industry stakeholders in the last few weeks**
- **Much of the material reiterated comments received in the open public comment period, which were already addressed by OEHHA**
- **We provide commentary in the next several slides on a few additional or embellished points at the request of the Chair and other members.**

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Nasal/Larynx Lesion (1)

- Questions raised about what is NOAEL, LOAEL from Reinhold study; changes seen are adaptive (versus adverse) and reversible
  - Some said none of the effects were adverse at any dose including clinical symptoms in rats
- Dr. Renne - Larynx lesions: metaplastic changes mild and reversible and therefore not adverse
- Dr. Renne - Nasal lesions: 2 highest levels, 70 and 243 mg/m^3 – increased effect of exposure; lack of complete 4-week recovery
  - Considered 24 mg/m^3 a NOAEL for nasal lesions

Response (1)

- We disagree that lesions and clinical symptoms are “nonadverse adaptive changes”
  - As noted in our response to comments, OEHHA considers mild inflammatory changes and lesions adverse; 24 mg/m^3 is a LOAEL, not a NOAEL
  - Reversibility irrelevant
  - OEHHA considers observed clinical symptoms including nasal discharge, moist rales, labored breathing, red staining of facial area as adverse.

Response (1, cont'd)

- **No need to argue about what is a NOAEL or a LOAEL if you employ the curve fitting models in the Benchmark dose program, finding the 95% UCL on the dose that produces a 5% response rate (as described in our methodology document)**
- **We applied the BMD program to the laryngeal lesions and to the nasal lesions (next slides) as another way of evaluating a point of departure for the REL.**

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Benchmark Concentration Results

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

- **$BMCL_{05}$** - 95% lower confidence limit of dose for a 5% response rate

Response (1, cont'd)
8-hr & Chronic REL Comparison

- POD is 4 mg/m^3 based on nasal respiratory mucosa lesions
- Dose and time adjustments are the same
- Uncertainty factors totaling 60 are the same

RELS based on nasal lesions:

- 8 Hour: 8.93 µg/m^3 or 9 µg/m^3
  1.93 ppb or 2 ppb
- Chronic: 2.98 µg/m^3 or 3 µg/m^3
  0.643 ppb or 0.6 ppb

Respiratory infection in rodents in Reinhold study

Some said there is no evidence of an infection in the Reinhold study rats, so OEHHA should not infer infection was present in the rats or responsible for lesions in controls

- **Response: We agree that there is not evidence of an infection and have removed phrase on page 24 which implies presence of infection.**

BMD model inappropriately applied to continuous data

One person thought we used a quantal model in the BMD model inappropriately for continuous data

- Response: We applied the quantal model to quantal incidence data of lesions in three regions of the upper airway. This is not a misapplication of the model.

Aerosol vs vapor comments

Should not use the Reinhold rat study because exposure was to an aerosol, not vapor.

- **Response: OEHHA used the best data available. We recognize that this introduces some uncertainty. However, it is not likely that the vapor phase caprolactam would have different toxicity than the aerosol phase as both would impact the upper airway the most, given the water solubility. We added some additional discussion to the document of this issue.**

RGDR dosimetry adjustment

The RGDR dosimetry adjustment is unnecessary for a point of contact irritant

- **Response: The RGDR is the method employed by USEPA for water soluble gases affecting the upper airway, such as caprolactam, to estimate the human equivalent concentration from experimental concentrations in animals.**

Ziegler study statistics

Dr. Haseman reviewed the statistics in Reinhold and our ranking of lesions to evaluate trend.

- **We agree with most of his comments on the Ziegler paper**
- **We agree that one needs the individual data for a proper evaluation of trends in the data**
- **We agree that the interdependence of the symptom questions in the questionnaire makes it difficult to analyze these data**
- **Dr. Haseman pointed out a few potential errors in the OEHHA document which we are evaluating and will fix if appropriate**

Time correction from experimental duration to human exposure duration

A few stated it is inappropriate to use time extrapolation for an irritant; another thought the UF for subchronic to chronic duration also unnecessary because irritants are concentration not time dependent.

- Response: OEHHA treats sensory irritants as concentration and not time dependent. However, the basis of the REL is not sensory irritation, but irritation producing tissue lesions which is both concentration and time dependent; time correction from 6 hr/d, 5d/wk to either 8hr/d, 7 d/wk (for the 8 hour REL) or a 24hr/d, 7 d/wk (for the chronic REL) is appropriate. Likewise the modest correction from a 13 week study as a basis for a continuous chronic REL is appropriate.

Intraspecies UF

Some indicated no need for an Intraspecies Uncertainty Factor of 10 to account for potential asthma exacerbation in children (per our approved methodology) because an upper airway irritant would not "trigger a lower airway symptom in a postulated susceptible population"

- **Response: An irritant need not reach the lower airway to trigger an asthma response; bronchoconstrictive airborne pollutants can be water soluble gases (e.g., sulfur dioxide, acetaldehyde)**

No need for interspecies uncertainty factor

There is no need for an interspecies UF because rat laryngeal tissues are more or equally sensitive to irritants than humans.

- Response: This default is used in the absence of chemical specific data, which is the case here; also whether one uses laryngeal lesions or nasal respiratory lesions, the REL is about the same.