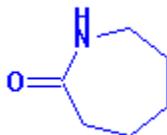


CAPROLACTAM

(VAPOR, DUST & AEROSOL)

(Aminocaproic lactam; epsilon-Caprolactam; Hexahydro-2H-azepin-2-one; 2-Oxohexamethylenimine; 2-Ketohexamethylenimine)

CAS 105-60-2



1. Summary

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)). OEHHA developed a Technical Support Document (TSD) in response to this statutory requirement that describes acute, 8-hour and chronic RELs and was adopted in December 2008. The TSD presents methodology reflecting the latest scientific knowledge and techniques, and in particular explicitly includes consideration of possible differential effects on the health of infants, children and other sensitive subpopulations, in accordance with the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, chapter 731, statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*). These guidelines have been used to develop the following REL for caprolactam: this document will be added to Appendix D of the TSD.

Exposure to caprolactam has been found to cause nasal, respiratory and eye irritation in both animals and humans. Exposure causes inflammation of the nasal and laryngeal epithelium in exposed rodents. High doses administered orally to pregnant rats caused fetal weight loss.

1.1 Acute REL Summary

<i>Acute inhalation reference exposure level</i>	50 $\mu\text{g}/\text{m}^3$ (3 ppb) as vapor
<i>Critical effect(s)</i>	Increased total symptom and complaint score, including nasal and eye irritation
<i>Hazard index target(s)</i>	Respiratory system; eyes

1.2 8-Hour REL Summary

<i>8-Hour Inhalation reference exposure level</i>	2 $\mu\text{g}/\text{m}^3$ (0.5 ppb) as aerosol
<i>Critical effect(s)</i>	Inflammatory changes of nasal and laryngeal epithelium

<i>Hazard index target(s)</i>	Respiratory system
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1.3 Chronic REL Summary

<i>Chronic inhalation reference exposure level</i>	0.8 $\mu\text{g}/\text{m}^3$ (0.2 ppb) as aerosol
<i>Critical effect(s)</i>	Inflammatory changes of nasal and laryngeal epithelium
<i>Hazard index target(s)</i>	Respiratory system

2. Physical and Chemical Properties (from HSDB (2006), unless noted otherwise)

<i>Description</i>	White, hygroscopic, crystalline solid or flakes with unpleasant odor
<i>Molecular formula</i>	$\text{C}_6\text{H}_{11}\text{NO}$
<i>Molecular weight</i>	133.16 g/mol
<i>Density</i>	1.05 g/cm ³ @ 25 °C
<i>Boiling point</i>	270 °C
<i>Melting point</i>	69.3 °C
<i>Vapor pressure</i>	0.0021 mm Hg @ 25 °C, equivalent to a saturated vapor concentration of about 13 mg/m ³ (Reinhold et al., 1998)
<i>Odor threshold</i>	0.3 mg/m ³ (Gross, 1984)
<i>Solubility</i>	Very soluble in water, benzene, diethyl ether, and ethanol. Soluble in chlorinated solvents, petroleum distillates, and cyclohexene
<i>Conversion factor</i>	1 ppm = 4.63 mg/m ³ (as vapor) @ 25° C

3. Occurrence and Major Uses

Caprolactam is the monomer used in the polymerization process to manufacture synthetic fibers and resins (particularly Nylon 6), bristles, film, and coatings (Cooper et al., 1993). Ninety-nine percent of all caprolactam is used to produce Nylon 6, which is used in a variety of products including carpets, furniture, apparel, appliance parts, and brush bristles (Cooper et al., 1993). Caprolactam is also used for the manufacture of synthetic leather, paint vehicles, polyamide plastics for packaging foodstuffs and other products, and for the synthesis of the amino acid lysine (IARC, 1999; Bradley et al., 2004).

For industrial processes, caprolactam is characterized as a solid at room temperatures, but with a significant vapor pressure (Ferguson and Wheeler, 1973). Nylon 6 manufacture using heated or molten caprolactam released caprolactam vapor during uncontrolled processes, which subsequently condensed into a fume in the workplace air (Kelman,

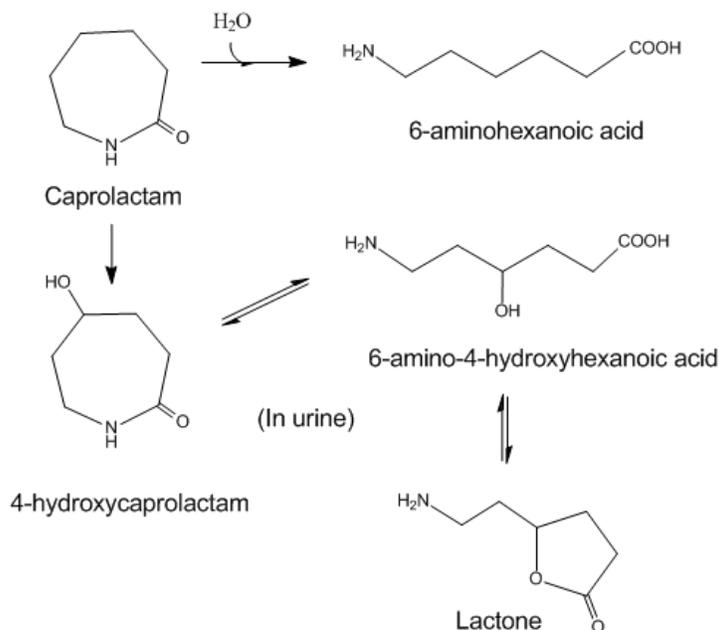
1986). Contact of the fume with cooler surfaces resulted in the formation of light feathery flakes. The IWMB (2003) reports that in the ambient environment, caprolactam would be expected to be in the vapor phase due to a vapor pressure of 0.0021 mm Hg @ 25 °C. However, Wilkins et al. (1993) found caprolactam in floor dust following a thermal desorption process to analyze VOC emission profiles. Thus, caprolactam also appears to bind to dust particles. Caprolactam has also been observed on fine aerosols in the atmosphere as a result of the probable release from a facility that uses caprolactam as a raw material (Cheng et al., 2006).

Measurable levels of caprolactam have been found primarily in indoor air as a result of release of the vapor or dust from carpeting containing Nylon 6 (IWMB, 2003). It is presumed that the polymerization process of caprolactam to nylon polymer may not be 100 percent efficient, thus allowing some of the un-polymerized caprolactam into the final product. Goldblatt et al. (1954) noted that the polymerized fiber contains approximately one percent of the caprolactam monomer. Lactam vapor contaminants found in Nylon 6 factories, mainly the dimer and trimer forms, may also be present in finished products.

Based on the measured emission rate of caprolactam from carpet samples, modeled air concentrations for office and classroom scenarios ranged from 39 to 450 $\mu\text{g}/\text{m}^3$ (IWMB, 2003). A chamber study found caprolactam emissions from polyamide and polypropylene carpets ranging from 6 to 97 $\mu\text{g}/\text{m}^3$ on the 28th day of chamber testing (Wilke et al., 2004). Caprolactam was detected in all floor dust samples collected during an indoor air study in nine public buildings (Wilkins et al., 1993). The emission rate of caprolactam following installation of a Nylon-6 broadloom carpet in a new California relocatable classroom was about 5 mg/h prior to occupancy, and dropped to 3 mg/h 27 weeks after first occupancy (Hodgson et al., 2004). The average caprolactam concentration in the classroom during school hours over 8 weeks following installation was 22.2 $\mu\text{g}/\text{m}^3$ (range: 10.6 - 30.1 $\mu\text{g}/\text{m}^3$). Similar relocatable classrooms that installed upgraded carpets containing Nylon-6,6, a fiber different from Nylon 6, emitted low to non-detectable concentrations of caprolactam (maximum: 1.4 $\mu\text{g}/\text{m}^3$).

4. Metabolism

In rats, approximately 16% of ingested caprolactam in diet was excreted in urine as 4-hydroxycaprolactam and a small amount as the non-hydroxylated acid, 6-aminohexanoic acid (Kirk et al., 1987). Following a single oral dose of [¹⁴C]caprolactam in male rats, 77.6% of the radioactivity was excreted in urine, 3.5% in the feces, and 1.5% in the expired air in 24 hrs (Unger et al., 1981). The half-life of disappearance of radioactivity from the blood was 2.98 hr. The radioactivity was excreted predominantly as two unidentified metabolites comprising 79.3 and 17.7% of the total urinary radioactivity. Unchanged caprolactam represented only 2.3% of the total urinary radioactivity. The radiolabeled caprolactam was widely distributed among the tissues of the rat with concentrations mostly similar to that in the blood. The radioactivity was consistently lower in fat relative to the blood in the first 24 hrs, indicating a low affinity of caprolactam and its metabolites for adipose tissue.

Figure 1. Metabolism of caprolactam

Oral delivery of [^{14}C]caprolactam in male and female mice also showed that the chemical is rapidly absorbed from the stomach and freely distributed into all tissues (Waddell et al., 1984). Almost all radioactivity was eliminated in 24 hours, although some retention of radioactivity during this time was noted in the nasal epithelium, olfactory lobe of the brain, liver, optic lens and Harderian gland. In pregnant mice, sites of localization of the radiolabel were identical to non-pregnant mice, with some residual radioactivity also noted in the umbilical cords, amnion, and yolk sac. No radioactivity was retained in any other fetal tissues. It was speculated that metabolism of caprolactam in the nasal tissue may produce a metabolite that was slow to clear.

5. Acute Toxicity of Caprolactam

5.1 Acute Toxicity to Human Adults

No studies were located regarding effects of human exposure to finished products emitting caprolactam in indoor air environments. Occupational exposure to caprolactam is known to cause dermal, eye and upper respiratory tract irritation but clear dose-response data are lacking (Kelman, 1986; Billmaier et al., 1992).

To address possible chemosensory effects of caprolactam at low concentrations reflecting the indoor environment, Ziegler et al. (2008) conducted chamber exposures of 20 human subjects to 0, 0.15, 0.5, and 5 mg/m³ caprolactam for 6 hours on 4 successive days. Irritation was assessed by questionnaire before and three times after exposure, and by measures of blinking frequency and assessment of conjunctival hyperemia based on digital

slit lamp photographs taken during exposure. Nasal resistance was measured by active anterior rhinometry before and after exposures. There were nonsignificant trends towards higher blink frequencies and increased nasal resistance with increasing caprolactam concentrations, but no evidence of change in eye redness. Questionnaires were used to evaluate 29 acute symptoms and to generate a total daily score. Questions assessed irritation to eyes, nose, throat and skin, as well as smell and taste perception, blurred vision, headache, and feelings of dizziness or weakness.

The questionnaires were administered after 1, 3 and 6 hours of exposure. In the low concentration range (0 – 0.5 mg/m³), there were no significant differences among scores. At 5 mg/m³ the total symptom scores were significantly elevated ($p \leq 0.05$). No statistically significant increase or decrease in the total symptom score was observed in the course of the day. Thus, the results do not indicate any adaptation or habituation processes in the course of the 6 hour exposure.

Subscores for ocular or nasal irritation and combined irritant response showed only nonsignificant trends by the ANOVA test towards increased irritation with increasing caprolactam concentrations. Caprolactam exposure was also associated with a statistically significant unpleasant odor even in the low concentration range of 0.15 mg/m³. However, the average intensity score of about 1.2 was only slightly pronounced at 5 mg/m³ (i.e., between “barely” (1) and “somewhat” (2) an odor nuisance).

The LOAEL and NOAEL for acute caprolactam exposure are 5 mg/m³ (1.1 ppm) and 0.5 mg/m³, respectively, for increased total symptom score. Benchmark concentration (BMC) analysis using U.S. EPA (2010) continuous modeling methodology was carried out for the dose-related increase in total symptom scores presented in graphical form by Ziegler et al. (2008). BMCs and BMCL₀₅s (the 95% lower confidence interval at the 5% response rate) could be calculated using Hill and exponential models and are shown in Table 1. The BMCL₀₅ is considered to be similar to a NOAEL in estimating a concentration associated with a low level of response. The p-values are smaller than 0.05, suggesting the model fit to the data is not appropriate to utilize this approach.

Table 1. BMC continuous model results for total symptom score at 1 hour of exposure to caprolactam.

Model	BMC (mg/m ³)	BMCL ₀₅ (mg/m ³)	P-value
Hill	0.31	0.18	0.037
Exponential	0.35	0.24	0.025

Modeling the eye and nasal irritation scores using the BMC software was not successful because the test for trend was not significant ($p > 0.05$), indicating the response differences between dose levels are not different and/or the variance among dose levels are too large.

Ferguson and Wheeler (1973) exposed 5 unacclimated workers briefly (on the order of seconds) to caprolactam vapor concentrations of 10, 14, 25, and 104 ppm (46, 65, 116, and 482 mg/m³, respectively) at a caprolactam plant. Most or all of the workers reported

transient nasal and throat irritation at all concentrations. Eye irritation was noted only in one volunteer at the highest concentration. The degree of discomfort felt by the workers was considered dose-responsive, but was not quantified. Some of the volunteers were exposed to similar concentrations for up to 30 min, but the sensory effects were not clearly stated or quantified. Brief exposure to 400-1200 ppm caprolactam was described as extremely irritating, resulting in a choking response.

Approximate 8-hr time-weighted average (TWA) air samples were collected from various locations in a work area over five days at two different caprolactam polymer facilities (Ferguson and Wheeler, 1973). The 8-hr TWA air concentrations of caprolactam vapor during working hours were 3.2 ppm (range = 1.3 to 6.9 ppm) at location 1, and 1.1 ppm (range = <0.5 to 4.5 ppm) at location 2. The workers reported no response with exposure to a concentration as high as 7 ppm. Based on the percent time worked in the caprolactam-contaminated rooms, the worker exposure durations were estimated to be about 15 to 45 min at location 1, and 1 to 4 hrs at location 2.

At a caprolactam monomer plant, Ferguson and Wheeler (1973) also conducted experimental exposures of worker volunteers and collected 8-hr TWA caprolactam vapor concentrations at various sites over a 3-week period. During experimental exposures of unspecified durations, no discomfort was noted at concentrations up to 14 ppm at a relative humidity was 100%. The concentration of caprolactam sampled at various worksite locations ranged from 0.2 to 17.6 ppm. Worker exposure durations in the caprolactam-contaminated areas ranged from 10 min to almost 3 hrs. Lack of irritant responses above 10 ppm was thought to be related to the higher relative humidity at the monomer plant, and/or possibly due to more uniform concentrations.

5.2 Acute Toxicity to Infants and Children

No studies were located regarding acute toxicity to infants and children exposed to caprolactam.

In animal studies, oral intubation of [¹⁴C]caprolactam in pregnant and non-pregnant mice showed that the chemical is rapidly absorbed from the stomach and freely distributed into all tissues, including the fetuses (Waddell et al., 1984). The kinetics of distribution and elimination appeared to be the same in male, female and pregnant animals, with almost all radioactivity eliminated within 24 hours. Although some retention of radioactivity during this time was noted in the umbilical cords, amnion, and yolk sac, the distribution into and removal from the fetuses was typical of molecules that diffuse freely across the placenta. There was no retention of radioactivity in any fetal tissue.

5.3 Acute Toxicity to Experimental Animals

Recent, peer-reviewed studies for acute caprolactam exposure in experimental animals are lacking. Four-hour exposure of rats to 5,250, 8,350, or 10,120 mg/m³ caprolactam aerosol

via a head-nose inhalation system resulted in eyelid closure, shallow to spasmodic breathing, and mild to strong defense reactions (BASF, 1985). After exposure, bloody nasal secretions, marked tremor, and bloody lacrimation were also observed. LC₅₀s of 9,600 and 7,080 mg/m³ were recorded for male and female rats, respectively. In rats that died, general circulatory congestion, elevated hyperemia of the lung, and moderate to severe fatty degeneration of the liver were found. No additional deaths occurred after one day post-exposure and all surviving animals appeared normal 3 days post-exposure.

In an unpublished study reported by the U.S. EPA (1998), guinea pigs were exposed for 0.5 hr on 5 consecutive days to 3, 10, or 30 mg/m³ aerosols generated from a 15% aqueous solution of caprolactam. Animals were monitored with whole-body plethysmography for indications of irritation, coughing, pulmonary hypersensitivity, and airway reactivity. No significant respiratory responses were noted at any concentration.

6. Chronic Toxicity of Caprolactam

6.1 Chronic Toxicity to Human Adults

Occupational exposure to caprolactam is known to cause dermal, eye and upper respiratory tract irritation with acute or recurrent acute exposure, but chronic toxicity data resulting from prolonged caprolactam exposure are lacking.

Ferguson and Wheeler (1973) indicated that working atmospheric concentrations of 7 ppm (32 mg/m³) or less at caprolactam polymer plants generally resulted in no discomfort of interviewed workers. In caprolactam monomer plants, eight-hour sampling of caprolactam vapor concentrations over a 3-week period in various work areas ranged from 0.2 to 17.6 ppm (0.9 to 81 mg/m³). Other than dermal injuries resulting from direct contact to concentrated caprolactam solutions, no general health problems requiring medical follow-up were found in a review of medical records collected during the 18 years of plant operation. In addition, no worker had been removed or asked to be removed from exposure to caprolactam vapor for health reasons during plant operation.

Kelman (1986) conducted a full clinical and occupational history of eight workers at a Nylon 6 manufacturing plant. Exposure was described as caprolactam vapor from heat-curing ovens, which subsequently condensed into a fume in the workplace air. Contact of the fume with cooler surfaces resulted in the formation of light feathery flakes. Average worker exposure was 4.8 years (range 9 months to 13 years) and mean atmospheric caprolactam dust concentrations at the time of the study were 84 mg/m³ (range 22-168 mg/m³) for static samplers and 68 mg/m³ (range 6-131 mg/m³) for personal samplers.

Recovery of caprolactam vapor from distilled-water bubblers was considered negligible. Several of the workers reported eye, nose, and throat irritation. All but one reported peeling of the skin on the hands. Kelman (1986) does not specifically state that the dermal irritation was due to direct contact with caprolactam, although Ferguson and Wheeler (1973) note that skin contact with caprolactam results in similar dermal irritation. Kelman

(1986) considered the lung function tests unremarkable when the smoking history of the workers was taken into account. Blood and urine samples were collected for assessment of hematological, hepatic and renal functions. No evidence of systemic toxicity was found.

Billmaier *et al.* (1992) compared medical records of 39 workers from two Nylon 6 manufacturing plants with mean work exposure of 18.7 years (range 8.2-31.7 years) against matched controls. Occasional personnel monitoring over a 10-year period at one plant showed daily caprolactam vapor concentrations averaged 3.7 mg/m^3 (0.8 ppm) with a range of 0.5 to 13.6 mg/m^3 (0.1 to 2.9 ppm) during sampling periods of 3 to 7.5 hrs. Sampling periods of 9-15 min during specific plant operations that represented maximum short-term exposures to caprolactam vapor ranged from 2.3 to 30.8 mg/m^3 (0.5 to 6.7 ppm) with an average of 17.2 mg/m^3 (3.7 ppm).

At the other plant, occasional personnel monitoring over a 10-year period resulted in an average daily caprolactam vapor exposure of 4.5 mg/m^3 (1.0 ppm) and a range of 0.5 to 10.3 mg/m^3 (0.1 to 2.2 ppm) during sampling periods of 3.3 to 7.3 hrs. Sampling periods of 15-59 min during specific plant operations that represented maximum short-term exposures to caprolactam vapor ranged from non-detectable to 34.8 mg/m^3 (0 to 7.5 ppm) with an average of 18 mg/m^3 (3.9 ppm).

Individual worker exposure histories of the Billmaier *et al.* (1992) study could not be clearly determined due to high variability in caprolactam levels and changes in job responsibilities throughout the workday. The monitoring method detected total caprolactam and did not differentiate between various states of the material, but the industrial processes involved indicated caprolactam was likely to be predominantly in the vapor state. Only a few episodes of injury or illness were noted in the medical records that were specifically related to caprolactam exposure. One employee reported dermatitis on two separate occasions, and another employee reported dermal irritation following direct exposure to a lactam-containing solution. A third employee complained of eye irritation on one occasion and reportedly inhaled partially polymerized nylon flakes on another occasion, leading to nausea. No specific caprolactam exposure-related nose or throat symptomatology was reported. It was unclear from these medical records if any of the injuries were due only to exposure to the vapor form of caprolactam. Pulmonary function tests were performed and compared to existing pulmonary function test data of the workers and to the control group. No exposure-related pulmonary function changes were observed, but it appears the spirometry performed was not in accordance with current guidelines and quality assurance procedures (USEPA, 1998).

In an oral exposure study, groups of obese patients received either placebo (n = 26), 3 g (n = 62) or 6 g (n = 28) of caprolactam daily as wafers or as tablets for 18 months to investigate the chemicals' weight reduction properties (Riedl *et al.*, 1963). In all instances, the patients were instructed to eat a 1000-calorie reducing diet. The subjects receiving the placebo showed no reduction in weight, while subjects treated with 3 and 6 gm caprolactam per day showed weight reductions averaging about 0.025 and 0.05 kg/day, respectively.

The patients that were administered caprolactam showed essentially no toxic effects; thirst was reported by one patient and a rash was observed in another patient. Factoring in body weights at the beginning of the study, average daily caprolactam intake of patients administered 3 g caprolactam daily was approximately 26 and 28 mg/kg body weight for males and females, respectively. The average daily intake of patients administered 6 g caprolactam was approximately 52 and 56 mg/kg body weight for males and females, respectively.

Riedl *et al.* (1963) also investigated the effects of caprolactam on intermediary metabolism when obese patients were administered 1 g glucose per kg body weight. Caprolactam treatment was not clearly specified, but appeared to also consist of 3 or 6 g doses per day for at least 2 months prior to glucose loading. Blood lactic acid levels were reduced in those patients receiving caprolactam. Blood sugar and levels of citric acid and non-esterified fatty acids in blood were unaffected by caprolactam treatment.

6.2 Chronic Toxicity to Infants and Children

No toxicity studies were located regarding prolonged animal exposure to caprolactam beginning at a young age.

In an animal three-generation developmental study, reductions in body weight and food consumption were not found in first-generation (P₁) rats exposed to caprolactam in feed, but were observed in the second- (P₂) and third-generation (P₃) rats treated with caprolactam (Serota *et al.*, 1988). The P₁ rats were young adults (approximately 6 weeks old) upon initiation of treatment. Since the P₂ and P₃ animals were exposed both *in utero* and through the early growth phase, the decreased body weights noted in the P₂ and P₃ animals were most likely due to the time of life in which treatment began.

6.3 Chronic Toxicity to Experimental Animals

Only a few multi-day or subchronic inhalation studies were found in the literature; no chronic inhalation studies have been performed.

Three guinea pigs exposed to 118 - 261 mg/m³ caprolactam dust for 7 hr/day for 7 days showed no adverse effects other than occasional cough (Goldblatt *et al.*, 1954). The majority of the caprolactam particles formed for the study were below 5 µm in size.

In a 13-week study, Sprague-Dawley CD rats were exposed to caprolactam aerosol (average mass median aerodynamic diameter = 3 µm; average geometric standard deviation = 1.7) at a concentration of 0, 24, 70, and 243 mg/m³ for 6 hours/day, 5 days/week (Reinhold *et al.*, 1998). A second group of rats was similarly exposed but sacrificed following a 4-week clean air recovery period. Treatment-related increases in respiratory (labored breathing) and secretory (nasal discharge) signs were noted in all groups during exposure, starting the second week and continuing through cessation of exposure at 13 weeks.

Weekly physical exams noted an exposure-related trend toward increased incidence of red staining (facial area), clear nasal discharge, and moist rales. At sacrifice, evidence of systemic toxicity and neurotoxicity was not found. Neurotoxicity evaluation was based on a functional observational battery conducted just prior to sacrifice consisting of tests for neuromuscular function and coordination, central nervous system activity and excitability, sensorimotor responses, and autonomic function. Ophthalmological examination did not find any treatment-related ocular changes in the rats.

Respiratory system changes in the 13-week exposure study were confined to nasoturbinal tissues and the larynx (Reinhold et al., 1998). Male and female responses were generally similar, so the data were combined. In the nasal mucosa, a dose-related trend for increased incidence and severity of intracytoplasmic eosinophilic material in the olfactory epithelium and goblet cell hypertrophy/hyperplasia in the respiratory epithelium was observed (Table 2). These olfactory and respiratory epithelial lesions were considered exposure-related at 70 and 243 mg/m³. The nasal mucosal changes were still apparent in the two highest exposure groups at the 4-week recovery sacrifice.

Laryngeal tissues showed a dose-related trend for increased incidence squamous/squamoid metaplasia/hyperplasia of the pseudostratified columnar epithelium covering the ventral seromucous gland, and were still evident in some animals of the two highest exposure groups following the 4-week recovery period. A few high exposure animals at terminal sacrifice had minimal keratinization of the metaplastic epithelium, but this finding was absent in the four-week recovery group.

Table 2. Incidences of microscopic findings of nasoturbinal and larynx lesions in the 13-week caprolactam exposure study in rats (Reinhold et al., 1998).

Endpoint ^a	Exposure Group (mg/m ³)			
	0	24	70	243
Nasal respiratory mucosa ^b	0/20	4/20	8/20	12/20
Nasal respiratory mucosa at 4-week recovery ^b	0/20	0/20	6/20	5/20
Nasal olfactory mucosa ^c	0/20	2/20	8/20	17/20
Nasal olfactory mucosa at 4-week recovery ^c	2/20	2/20	7/20	19/20
Laryngeal tissue ^d	0/20	5/20	12/20	20/20
Laryngeal tissue at 4-week recovery ^d	0/20	0/20	1/20	3/20
Keratinized metaplastic epithelium of larynx ^e	0/20	0/20	0/20	5/20

^a Nasal and larynx endpoints were categorically graded by a pathologist, on a scale from lowest to highest severity, as minimal, slight, moderate, or moderately severe. Statistical analysis of the pathology findings was not presented.

^b Goblet cell hypertrophy/hyperplasia - moderate changes only; minimal and slight changes were at background levels

^c Intracytoplasmic eosinophilic material – including slight, moderate, and moderately severe changes

^d Squamous/squamoid, metaplasia/hyperplasia – minimal and slight changes only at terminal sacrifice, and minimal changes only at 4-week recovery

^e Minimal changes only

Benchmark concentration (BMC) analysis was performed on the dose-related respiratory endpoints shown in Table 2 using benchmark dose modeling software supplied by U.S.

EPA (2003). BMCL₀₅s (the 95% lower confidence interval at the 5% response rate) for the nasal respiratory and olfactory changes and the non-keratinized laryngeal tissue changes found at terminal sacrifice are shown in Table 3. The BMCL₀₅ is considered to be similar to a NOAEL in estimating a concentration associated with a low level of response. For each endpoint, the BMCL₀₅ was derived from the models that provided the best visual and statistical fit to the data, particularly in the low dose region of the line where the BMCL₀₅ resides. Following U.S. EPA guidelines, the model with the lowest AIC (Akaike information criterion) was chosen in instances where various model fits to the data were similar.

Table 3. BMCL₀₅s for the toxic endpoints in the 13-week inhalation exposure study in rats (Reinhold et al., 1999).

Endpoint	BMCL ₀₅ (model)
Nasal respiratory mucosa changes	4 mg/m ³ (log-logistic)
Nasal olfactory mucosa changes	12 mg/m ³ (log-probit)
Laryngeal tissue changes	3 mg/m ³ (multistage)

A two-year caprolactam carcinogenesis bioassay feeding study was conducted by the NTP (1982). Caprolactam was incorporated in the diet of male and female rats at concentrations of 3,750 ppm or 7,500 ppm, and in the diet of male and female mice at concentrations of 7,500 and 15,000 ppm. Mean body weights of all dosed groups were decreased compared to their respective control groups throughout the two-year study. Feed consumption was inversely related to dose in rats, but caprolactam in the feed of mice had no effect on feed consumption. Growth curves for rats and mice are presented in graphical form by the NTP, but statistical analysis on mean body weight gain and feed consumption was not performed. The NTP concluded that the dose-related decrements in mean body weight gains indicate that it is highly likely that animals in the study were receiving the maximum tolerated doses of caprolactam.

Histopathologic examination did not find any compound-related effects in nasal tissues, larynx, esophagus, stomach, or any other tissues and organs. Table 4 presents the estimated range of daily caprolactam intake in feed, assuming 100% absorption, for each dose group during the study.

Table 4. Estimated range of daily intake of caprolactam in mg/kg body weight during a two-year feeding study (NTP, 1982).

Species	Males		Females	
	Low Dose	High Dose	Low Dose	High Dose
Rat	397 – 207 ^a	673 - 404	370 - 263	673 - 441
Mouse	1122 - 792	2442 - 2155	1796 - 1203	3907 - 3140

^a Caprolactam intake range for each dose group of each species was based on week 4 feed consumption (the period of time with the highest mg/kg body weight intake) and during a week in the second year of the study with the lowest mg/kg body weight intake.

7. Developmental and Reproductive Toxicity

No studies were located investigating the developmental and reproductive toxicity of caprolactam by the inhalation route.

In oral exposure studies, pregnant rats were dosed by gavage with caprolactam at 100, 500, or 1,000 mg/kg/day on gestation days 6-15 (Gad et al., 1987). Increased maternal mortality was observed at the highest dose. A dose-related decrease in mean maternal body weight was observed with a statistically significant reduction ($p \leq 0.05$) in total body weight at the highest dose level (a 10 and 11% reduction on gestational days 15 and 20, respectively). A statistically significant reduction ($p \leq 0.05$) in mean weight change was observed during the treatment period at the two highest doses (5.2 and 2.3% mean weight gain at the mid- and high-dose, respectively, compared to a 13.4% weight gain for the control group). Food consumption was reduced in the two highest dose groups. The mean incidence of resorptions was increased at the highest dose.

No dose-related skeletal anomalies or major malformations were noted among the offspring of any exposure group. An apparent dose-related increase in the mean number of skeletal variants per litter was observed, including incomplete ossification of the skull or vertebral column and the presence of extra ribs. However, no statistically significant difference in skeletal variation values between treated groups and the control group were noted.

Gad et al. (1987) also dosed pregnant rabbits by gavage with caprolactam at 50, 150, or 250 mg/kg/day on gestational days 6-28. Sixteen percent mortality and statistically significant decreased overall maternal body weight gain were observed at the highest dose. Corrected weight gain (i.e., weight gain minus weight of gravid uterus) was statistically significantly lower ($p < 0.05$) from day 6 to 29 of gestation in the 150 mg/kg group. Absolute maternal body weights were unaffected in this mid-dose group. Mean fetal weights were statistically significantly reduced ($p < 0.05$) by 12% in each of the two highest dose groups compared to controls. The incidence of major malformations was unaffected by caprolactam treatment. Minor skeletal anomalies included an increased incidence of unilateral or bilateral thirteenth ribs in the highest dose group.

Gad et al. (1987) concluded that caprolactam given by gavage to two species up to levels that caused severe maternal toxicity did not support a finding of the compound causing either embryotoxicity or teratogenicity. Fetotoxicity was evidenced in rabbits by lower fetal weights at the two highest doses, and an increased incidence of 13th ribs at the highest dose level.

In a multi-generation study, rats were given 1,000, 5,000, or 10,000 mg caprolactam/kg diet (ppm) over three generations (Serota et al., 1988). Each generation was treated over a 10-week period. Consistently lower mean body weights and food consumption were observed in both P₂ and P₃ parental generations at 5,000 and 10,000 ppm, but body weights were unaffected in P₁ animals at all dose levels. The mean body weight changes were statistically significant ($p \leq 0.05$) in all high dose groups at all time points with weight

reductions in both males and females ranging from 10 to 21% compared to controls. For mid-dose animals, a statistically significant change in mean body weight occurred only in P₂ males, a 13% reduction compared to controls, during week four of exposure.

Dose-related reductions of fetal body weights were observed in all filial generations. For example, statistically significant differences ($p \leq 0.05$) noted in F_{1a} and F_{1b} high dose groups (17 to 23% reductions compared to controls) and occasionally in mid-dose groups (11 to 14% reductions in F_{1b} offspring only compared to controls). Based on mean body weight and mean food consumption values at week 10 in P₁ females, caprolactam in the diet at 1000, 5000 and 10,000 ppm was equivalent to a daily dose of 697, 3542 and 5622 mg/kg caprolactam, respectively.

No treatment-related effect on gross appearance, gross pathology, survival rate or number of pups was observed. A slight increase in the severity of spontaneous nephropathy was observed on histopathologic examination of males in the high-dose group of the first parental generation.

Serota et al. (1988) concluded that caprolactam in the diet at the two highest exposures resulted in decreases in body weight in both pups and parental animals in utero through weaning. Similar effects on food consumption were also noted. Body weights were unaffected in P₁ animals at all dose levels, and reduced food consumption was observed only at week 10 in P₁ females. No effects were evident on reproductive performance or offspring survival, and only minimal kidney toxicity was observed in males at the highest dose level.

In other oral exposure studies, male mice treated with 222, 333, 500, 750, or 1,125 mg/kg caprolactam by gavage daily for five days did not result in abnormal sperm, although mortality was observed at the three highest doses (Salamone, 1989). A similar study in male rats did not observe DNA damage to spermatocytes following an oral dose of 750 mg/kg caprolactam (Working, 1989).

The primary finding of the two developmental/reproduction oral exposure studies was that caprolactam may be fetotoxic due to reduced fetal body weight. Reductions in fetal weight in the gavage study occurred at the same dose levels that reductions in maternal food consumption and body weight occurred. Based on this gavage study, the concomitant reduction in both maternal body weight and fetal weight make it difficult for OEHHA to conclude that caprolactam is exclusively fetotoxic. However, body weights of P₁ rats in the multi-generation study were not reduced by caprolactam exposure yet resulted in reduced fetal weights in F_{1a} and F_{1b} offspring. This finding indicates a fetotoxic LOAEL of 5000 ppm caprolactam in feed, which is equivalent to a maternal daily dose of 3542 mg/kg. The calculated NOAEL is 697 mg/kg.

Assuming 100% pulmonary absorption, the NOAEL is equivalent to an air concentration of 2440 mg/m³ (697 mg/kg x 70 kg body wt. / 20 m³/day) in a route-to-route extrapolation. Brief human exposures to lower caprolactam concentrations in the range of 1850 to 5560 mg/m³ (400 to 1200 ppm) has been characterized as extremely irritating, and

subchronic exposures of rats to air concentrations as low as 24 mg/m³ have resulted in labored breathing and nasal secretory discharge. Applying a standard 1000-fold uncertainty factor for extrapolation from an animal developmental study to human exposure would produce a proposed REL of 2.4 mg/m³. The acute REL of 50 µg/m³ derived from a human exposure study is lower than that derived from the oral multi-generation animal study.

These findings show that the oral dose at which fetotoxicity occurs is likely not relevant to air concentrations of caprolactam for REL derivation due to severe pulmonary injury occurring at much lower concentrations. In addition, the acute, 8-hour and chronic RELs developed in this document based on caprolactam air exposures would be protective for reproductive/developmental effects. Therefore, OEHHA is using pulmonary and sensory irritation endpoints for the caprolactam inhalation RELs.

8. REL Derivations

8.1 Derivation of the Acute Air Reference Exposure Level (1-hour exposure)

<i>Study</i>	Ziegler et al., 2008
<i>Study population</i>	20 human adults: 10 male, 10 female
<i>Exposure method</i>	Whole body chamber
<i>Exposure duration</i>	6 hr
<i>Critical effects</i>	Total symptom score including nasal/eye irritation
<i>LOAEL</i>	5 mg/m ³
<i>NOAEL</i>	0.5 mg/m ³ (recommended point of departure)
<i>Time adjusted exposure</i>	0.5 mg/m ³ (irritant: no time adjustment applied)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1 (default: human study)
<i>Toxicodynamic (UF_{A-d})</i>	1 (default: human study)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (site of contact; no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Acute air reference exposure level</i>	0.05 mg/m ³ (3 ppb)

The NOAEL in this study was 0.5 mg/m³, the highest concentration at which the total symptom scores were not significantly elevated. No time adjustment is applied since sensory irritation is generally dependent more on concentration than on time. Since the study was performed in humans, no interspecies adjustments are required. Little intraspecies toxicokinetic variation among individuals is expected with the acute irritant response to caprolactam so no UF is applied. While caprolactam is irritating to the upper respiratory tract, initiation or exacerbation of asthma has not been characterized for this compound. No data were located to ascertain if children or other groups might be differentially susceptible during acute exposure to caprolactam. Therefore, a UF of 10 is applied to address the potential variation in the intraspecies toxicodynamic response, including child/adult asthmatic responses to an irritant. This should ensure protection of children's health. The cumulative UF is 10 and the acute REL is 0.05 mg/m³ (50 µg/m³).

We evaluated the use of the benchmark dose method to derive an acute REL. However, as noted earlier the low p-values (p<0.05) for data fit using the BMC models suggest that the NOAEL/LOAEL approach is more appropriate.

8.2 Derivation of the 8-Hour Air Reference Exposure Level

<i>Study</i>	Reinhold et al. 1998
<i>Study population</i>	Sprague-Dawley CD rats (10 animals/sex/group)
<i>Exposure method</i>	Discontinuous whole-body inhalation exposure to 0, 24, 70, and 243 mg/m ³ caprolactam aerosol
<i>Critical effects</i>	Upper airway lesions of nasal and laryngeal epithelium
<i>LOAEL</i>	24 mg/m ³
<i>NOAEL</i>	Not observed
<i>BMCL₀₅</i>	3 mg/m ³
<i>Exposure continuity</i>	6 hours per day, 5 days/week
<i>Exposure duration</i>	13 weeks
<i>Average experimental exposure</i>	1.607 mg/m ³ (3 mg/m ³ x 6/8 x 5/7)
<i>Human equivalent concentration</i>	0.2443 mg/m ³ (aerosol with extrathoracic respiratory effects, RDDR = 0.152 based on MV = 0.14 L/min (ave. male rat), MMAD = 3 μm per Reinhold et al. (1998))
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	√10 (≤13 wk exposure in rodents)
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1
<i>Toxicodynamic (UF_{A-d})</i>	√10 (default: no interspecies toxicodynamic data)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (site of contact; no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>8-Hour air reference exposure level</i>	0.002 mg/m ³ (0.5 ppb)

The 8-hr REL derivation is based on a BMCL₀₅ = 3 mg/m³ for minimal and slight increases in squamous/squamoid metaplasia/hyperplasia in the larynx of male and female rats exposed to caprolactam aerosol for 13 weeks (Reinhold et al., 1998). Male and female responses were similar, so were combined to increase the strength of the BMC analysis. BMCL₀₅s were also derived for lesions of the olfactory (BMCL₀₅ = 12 mg/m³) and respiratory (BMCL₀₅ = 4 mg/m³) nasal mucosa.

Reinhold *et al.* (1998) regarded laryngeal keratinization of the metaplastic epithelium to be the primary adverse effect, resulting in a NOAEL of 70 mg/m³. The other effects in the upper respiratory system were considered by the researchers to be normal adaptive responses to an irritant, which were not considered a toxicological endpoint. However, under OEHHA guidelines the RELs include health protection against mild irritant/inflammatory effects. The irritant-related microscopic changes in the upper respiratory tract, combined with the observations of respiratory inflammation (nasal discharge) and labored breathing in all caprolactam-treated groups, supports the lack of an observed NOAEL in the principal study.

The $BMCL_{05} = 3 \text{ mg/m}^3$ was adjusted to an average experimental exposure of 1.6 mg/m^3 for eight-hour exposures, seven days/week. The regional deposited dose ratio (RDDR) of 0.152 was calculated using US EPA methodology (OEHHA, 2000) for extrapolation from rat and human exposure. A subchronic $UF = \sqrt{10}$ was incorporated into the REL derivation for extrapolation to chronic exposure. Measurable indoor air levels of caprolactam have been found in classrooms with Nylon-6 carpets over an 8-week period following first occupancy (Hodgson et al., 2004). However, the emission rate of caprolactam from the Nylon 6-containing carpets had lowered only about 40% 27 weeks following first occupancy, suggesting potential long-term, low-level exposure.

An interspecies UF was not applied for toxicokinetic differences. Hybrid computational fluid dynamics and PBPK modeling for predicting nasal tissue dose metrics show that the predicted dose to the epithelium of the total nasal cavity following inhalation of an organic gas is similar, or slightly greater, in humans compared to rats (Frederick et al., 2001). Also, the rather indiscriminant nature of the injury to different regions of the upper respiratory tract indicates that caprolactam is primarily a direct-acting irritant, rather than a chemical requiring metabolic activation in nasal mucosa to cause tissue injury (Kilgour et al., 2000). Therefore, the human equivalency concentration (HEC) adjustment for upper respiratory tract injury should also be sufficient for any residual interspecies toxicokinetics differences.

The available toxicokinetic data for inspired caprolactam in humans suggest low interindividual variation, so no intraspecies toxicokinetic UF is assigned. While caprolactam is irritating to the upper respiratory tract, initiation or exacerbation of asthma by caprolactam has not been characterized. Thus, an intraspecies toxicodynamic UF of 10 is applied to address the diversity in the human population, including children. Application of the cumulative $UF = 100$ to the human equivalent concentration of 0.24 mg/m^3 resulted in an 8-hour REL of 0.002 mg/m^3 ($2 \text{ } \mu\text{g/m}^3$) for caprolactam.

8.3 Derivation of the Chronic Air Reference Exposure Level

<i>Study</i>	Reinhold et al. 1998
<i>Study population</i>	Sprague-Dawley CD rats (10 animals/sex/group)
<i>Exposure method</i>	Discontinuous whole-body inhalation exposure to 0, 24, 70, and 243 mg/m ³ caprolactam aerosol
<i>Critical effects</i>	Upper airway lesions of nasal and laryngeal epithelium
<i>LOAEL</i>	24 mg/m ³
<i>NOAEL</i>	Not observed
<i>BMCL₀₅</i>	3 mg/m ³
<i>Exposure continuity</i>	6 hours per day, 5 days/week
<i>Exposure duration</i>	13 weeks
<i>Average experimental exposure</i>	0.5357 mg/m ³ (3 mg/m ³ x 6/24 hr x 5/7 days)
<i>Human equivalent concentration</i>	0.08143 mg/m ³ (aerosol with extrathoracic respiratory effects, RDDR = 0.152 based on MV = 0.14 L/min (ave. male rat), MMAD = 3 μm per Reinhold et al. (1998))
<i>LOAEL uncertainty factor</i>	1
<i>Subchronic uncertainty factor</i>	√10 (≤13 wk exposure in rodents)
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{A-k})</i>	1
<i>Toxicodynamic (UF_{A-d})</i>	√10 (default: no interspecies toxicodynamic data)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF_{H-k})</i>	1 (site of contact; no systemic effects)
<i>Toxicodynamic (UF_{H-d})</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Chronic reference exposure level</i>	0.0008 mg/m ³ (0.2 ppb)

The chronic REL is based on the same study as the 8-hr REL. The chronic REL derivation is the same as that used for the 8-hr REL, with the exception that the average experimental exposure is based on continuous, 24 hr/day exposure. The resulting human equivalent concentration is reduced to 0.08 mg/m³. The application of uncertainty factors was the same for both 8-hr and chronic RELs, resulting in a chronic REL = 0.0008 mg/m³ (0.2 ppb).

8.4 Data Strengths and Limitations for Development of the REL

Significant strengths for the caprolactam REL include (1) the use of a well-conducted animal study with histopathological analysis and (2) independent studies demonstrating comparable key irritant effects (nasal and throat irritation) in humans and experimental animals. Major areas of uncertainty are (1) the lack of comprehensive human inhalation dose-response data for long-term exposures, (2) no inhalation developmental/reproduction toxicity data, although sufficient oral developmental/reproduction data exist. (However, when converted to an air concentration, the level that causes fetotoxicity is considerably greater than the level that results in severe pulmonary injury), (3) the absence of a

NOAEL in the subchronic study, and (4) the paucity of chronic animal inhalation exposure studies in more than one species (5) lack of data on the effects of early-in-life exposure.

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