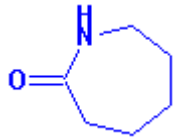
CAPROLACTAM
(VAPOR, DUST & AEROSOL)

(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 RELs for caprolactam: this document will be added to Appendix D of the TSD.

Exposure to caprolactam has been found to cause upper respiratory and eye irritation in both animals and humans. Exposure causes inflammation of the nasal and laryngeal epithelium in exposed rodents. The site-of-contact nature of the injury to 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). Although there is no evidence for reproductive or developmental effects at levels that produce sensory irritation, considerably higher doses administered orally to pregnant rats have resulted in reduced weight of offspring. Literature summarized and referenced in this document covers the relevant published literature for caprolactam through Fall 2010.

1.1 Acute REL Summary

Acute inhalation reference exposure level	**770 μg/m^3 (170 ppb)**
Critical effect(s)	Nasal and throat irritation in humans
Hazard index target(s)	Upper respiratory system

1.2 8-Hour REL Summary

8-Hour inhalation reference exposure level	**7 µg/m^3 (1 ppb)**
Critical effect(s)	Inflammatory changes of nasal and laryngeal epithelium in rodents
Hazard index target(s)	Upper respiratory system

1.3 Chronic REL Summary

Chronic inhalation reference exposure level	**2 µg/m^3 (0.5 ppb)**
Critical effect(s)	Inflammatory changes of nasal and laryngeal epithelium in rodents
Hazard index target(s)	Upper respiratory system

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

Description	A semi-volatile white, hygroscopic, crystalline solid or flakes with unpleasant odor
Molecular formula	$C_6H_{11}NO$
Molecular weight	133.16 g/mol
Density	1.05 g/cm^3 @ 25 °C
Boiling point	270 °C
Melting point	69.3 °C
Vapor pressure	0.001 mm Hg @ 20ºC (68ºF) 0.0021 mm Hg @ 25°C (77ºF), saturated vapor concentration = 13 mg/m^3
Odor threshold	0.3 mg/m^3 (Gross, 1984)
Solubility	Very soluble in water, benzene, diethyl ether, and ethanol. Soluble in chlorinated solvents, petroleum distillates, and cyclohexene
Conversion factor	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). Kelman (1986) reported that Nylon 6 manufacture using heated or molten caprolactam releases caprolactam vapor during uncontrolled processes, which subsequently condenses into a fume in the workplace air. Contact of the fume with cooler surfaces results 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.

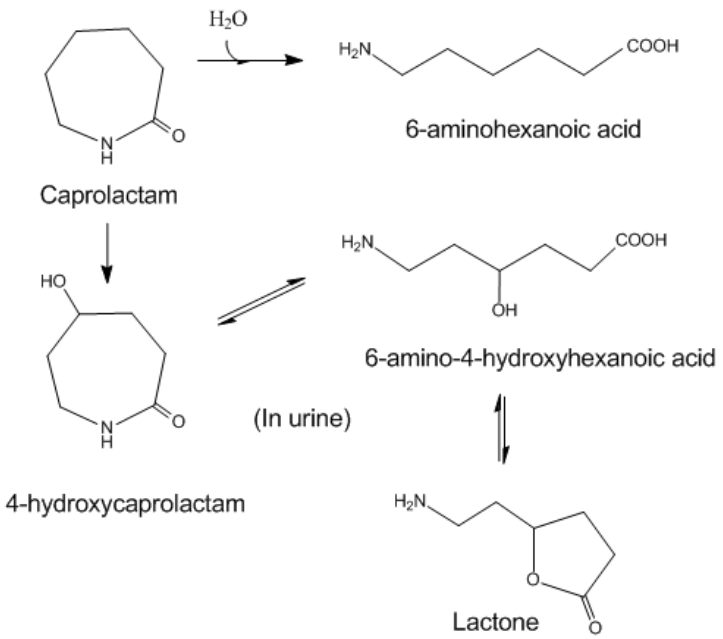
Based on the measured emission rate of caprolactam from carpet samples, modeled air concentrations for office and classroom scenarios ranged from 39 to 450 $\mu g/m^3$ (IWMB, 2003). A chamber study found caprolactam emissions from polyamide and polypropylene carpets ranging from 6 to 97 $\mu g/m^3$ on 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 $\mu g/m^3$ (range: 10.6 - 30.1 $\mu g/m^3$). 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 $\mu g/m^3$).

4. Metabolism

In rats, Kirk et al. (1987) observed that 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 (Figure 1). Following a single oral dose of [^{14}C]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 Adult Humans

No published studies have been conducted specifically examining toxicological effects of caprolactam from finished products that contain the chemical (e.g., finished Nylon 6 carpets). Occupational exposure to the monomer caprolactam prior to formation of Nylon 6 fibers or during the polymerization process to form the fibers is known to cause dermal, eye and upper respiratory tract irritation. Two published studies, a chamber exposure

study by Zeigler et al. (2008) and an industrial study by Ferguson and Wheeler (1973), examined the acute sensory irritant effects of caprolactam in humans.

Ferguson and Wheeler (1973) exposed 5 unacclimated workers at a caprolactam monomer plant to caprolactam vapor concentrations of 10, 14, 25, and 104 ppm (46, 65, 116, and 482 mg/m^3, respectively) while they were standing or conversing for several minutes downwind from a known emission source. The smoking status of the workers was not reported. Most or all of the workers reported transient nasal and throat irritation at all concentrations, including 4 out of 5 exposed individuals reporting irritation at 10 ppm (46 mg/m^3). 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 due to wide differences in the degree of discomfort between individual subjects. 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 (14.8 mg/m^3) with a range of 1.3 to 6.9 ppm (6.0 to 31.9 mg/m^3) at location 1, and 1.1 ppm with a range of <0.5 to 4.5 ppm (<2.3 to 20.8 mg/m^3) at location 2. No response with exposure to a concentration as high as 7 ppm (32 mg/m^3) was reported. Based on the percent time worked in specific locations of 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 (65 mg/m^3) at a relative humidity of 100%. The concentration of caprolactam sampled at various worksite locations ranged from 0.2 to 17.6 ppm (0.9 to 81.5 mg/m^3). Worker exposure durations in the caprolactam-contaminated areas ranged from 10 min to almost 3 hrs. Lack of irritant responses above 10 ppm (46 mg/m^3) was thought to be related to the higher relative humidity at the monomer plant, and/or possibly due to more uniform concentrations.

The authors concluded that the irritant response threshold for the workers is at or near 10 ppm (46 mg/m^3) caprolactam, and that 5 ppm (23 mg/m^3) is 50% of the "discomfort" threshold and "somewhat below the no-effect level". The authors state that additional support for their worker threshold value of 5 ppm is based on no reported distress in active and semi-active areas at concentrations up to about 7 ppm.

To address possible chemosensory effects of caprolactam at low concentrations reflecting the indoor environment, Ziegler et al. (2008) conducted chamber exposures of 20 adult subjects (10 men and 10 women) to 0, 0.15, 0.5, and 5 mg/m^3 caprolactam vapor for 6

hours on 4 successive days. Chemosensory effects were assessed by questionnaire, by measures of blinking frequency and assessment of conjunctival hyperemia based on digital slit lamp photographs taken during exposure, and by measures of nasal resistance using active anterior rhinometry before and after exposures. They observed 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 before exposure and after 1, 3 and 6 hours of exposure. Discounting odor nuisance, there were no significant differences among scores in the low concentration range of 0 – 0.5 mg/m^3 (Table 1). At 5 mg/m^3 the total symptom score of 29 acute symptoms was 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. Caprolactam exposure was also associated with a statistically significant increase in the subjects' detection of an unpleasant odor even in the low concentration range of 0.15 mg/m^3. However, the average intensity score of about 1.2 was only slightly pronounced at 5 mg/m^3 (i.e., between "barely" (1) and "somewhat" (2) an odor nuisance).

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 (Table 1).

Table 1. Mean ± standard deviation for eye and nose irritation scores, total symptom scores for chemosensory irritation, odor nuisance scores, and total symptom and complaint scores (Ziegler et al., 2008)[a].

	Caprolactam concentration in mg/m^3				ANOVA
	0	0.15	0.5	5.0	
Eye irritation	0.23 ± 0.26	0.32 ± 0.47	0.35 ± 0.41	0.38 ± 0.40	$P > 0.05$
Nose irritation	0.16 ± 0.20	0.17 ± 0.27	0.18 ± 0.24	0.26 ± 0.29	$P > 0.05$
Total irritation	0.19 ± 0.21	0.25 ± 0.36	0.27 ± 0.29	0.32 ± 0.33	$P > 0.05$
Odor nuisance[b]	0.10 ± 0.04	0.28 ± 0.08*	0.32 ± 0.08*	1.20 ± 0.19*	nd
Total symptom & complaint[b]	0.12 ± 0.03	0.18 ± 0.06	0.20 ± 0.05	0.36 ± 0.06*	nd

[a] Score ratings were: (0) not at all, (1) barely, (2) somewhat, (3) quite pronounced, (4) severe, and (5) very severe.
[b] Mean and standard deviation scores estimated from graphed data
nd = not determined
*$p \leq 0.05$ for paired t test

Additional statistical modeling of the eye and nasal irritation scores by OEHHA using the benchmark concentration (BMC) software (USEPA, 2010) was not successful. 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 is too large.

BMC analysis was also carried out using U.S. EPA (2010) continuous modeling methodology for the dose-related increase in total symptom scores presented in graphical form by Ziegler et al. (2008). BMCs and $BMCL_{05}$s (the 95% lower confidence interval at the 5% response rate) could be calculated using Hill and exponential models and are shown in Table 2. The p-values for model fit to the data are smaller than 0.05, suggesting the model fit to the data is not appropriate to utilize this approach.

Table 2. BMC continuous model results for total symptom and complaint 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

5.2 Acute Toxicity to Infants and Children

No studies were located regarding acute toxicity to infants and children exposed to caprolactam. We found no studies of inhalation exposure to young or pregnant animals that could shed insight into acute toxicity in infants and children.

5.3 Acute Toxicity to Experimental Animals

Relatively few peer-reviewed studies of acute caprolactam exposure in experimental animals have been conducted. Four-hour exposure of rats to 5,250, 8,350, or 10,120 mg/m^3 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. LC_{50}s of 9,600 and 7,080 mg/m^3 were recorded for male and female rats, respectively. In rats that died, general circulatory congestion, elevated hyperemia of the lung, moderate to severe fatty degeneration of the liver, and ischemic tubular nephrosis in the kidney cortex were found. No additional deaths occurred after one day post-exposure and all surviving animals appeared normal 3 days post-exposure. Histopathological examination of the organs in surviving rats 14 days post-exposure was unremarkable.

The U. S. Consumer Product Safety Commission conducted a study of sensory and pulmonary irritation in Swiss-Webster mice exposed to compounds emitted from carpet and carpet-related products, including caprolactam (CPSC, 1996). The animals were placed in a head-only glass plethysmograph and exposed to 13.5 mg/m^3 caprolactam vapor, the highest attainable exposure concentration. The methodology called for a one hour exposure, followed by a recovery period of 15 minutes in clean air, then exposure to the same concentration of caprolactam for another hour.

Sensory irritation is indicated when the group of mice showed a 12% or greater decrease in the mean respiratory frequency, the minimum level of respiratory depression needed to

classify an exposure as having a positive sensory irritation response (CPSC, 1996). By this approach, no measurable sensory irritation or reduction in respiratory rate was observed in the mice during the caprolactam exposure. However, the CPSC (1996) notes that measurable respiratory irritation in mice using this method usually occurs at levels 10 to 100 times higher than levels which would result in irritation in humans.

A similar study, although unpublished, was conducted in guinea pigs by Alarie and Stock (1990) and reported by the U.S. EPA (1998). The animals were exposed for 0.5 hr on 5 consecutive days to 3, 10, or 30 mg/m^3 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. Similar to the findings in mice, no significant respiratory responses were noted at any concentration.

6. Chronic Toxicity of Caprolactam

6.1 Chronic Toxicity to Adult Humans

Occupational exposure to caprolactam is known to cause dermal, eye and upper respiratory tract irritation with acute or recurrent acute exposure, but data on chronic toxicity endpoints resulting from prolonged caprolactam exposure in workers were considered by OEHHA to be inadequate for use as the basis of a chronic REL.

End of shift complaints by workers exposed to caprolactam at a factory included irritability, nervousness, heartburn, bloating, nose bleeds, upper airway inflammation, and dry and chapped lips and noses (Hohensee, 1951). Exposure included both the vapor and crystal, or dust, forms of caprolactam. Headache in response to the odor and unpleasant taste of the caprolactam vapor was also reported. All these symptoms subsided after a short (but unspecified duration) stay in fresh air. Factory inspection of the caprolactam concentration in the spinning room revealed a concentration of 61 mg/m^3, while the concentration in the laboratory room was 16-17 mg/m^3.

Ferguson and Wheeler (1973) indicated that working atmospheric concentrations of 7 ppm (32 mg/m^3) 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 81.5 mg/m^3). 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.

There are significant deficiencies in the Ferguson and Wheeler report that prevent it from use as the basis of an OEHHA chronic REL. As also noted by the U.S. EPA RfD/RfC Work Group, significant deficiencies included lack of information on the number of workers and the average duration and distribution of exposure (USEPA, 1998). Also, no

historical air levels are given, all exposures are determined from area rather than personal samplers, and no attempt was made to reconstruct individual exposure histories.

Kelman (1986) conducted a clinical and occupational history of eight workers, seven of which were smokers, 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/m^3 (range: 22-168 mg/m^3) for static samplers and 68 mg/m^3 (range: 6-131 mg/m^3) for personal samplers. The caprolactam dose and exposure durations for individual workers were not provided. Recovery of caprolactam vapor from distilled-water bubblers was considered negligible, which the authors interpreted as indicating exposure was limited to caprolactam dust.

Kelman (1986) reported that several of the workers (number not given) complained of “some degree” of eye, nose, and throat irritation. It was unclear from the study if the irritation was chronic in nature. All but one reported peeling of the skin on the hands. Although the study does not specifically state that the dermal irritation was due to direct contact with caprolactam, Ferguson and Wheeler (1973) note that skin contact with caprolactam results in a similar dermal injury. Five workers showed abnormal maximal expiratory flow volumes. However, the author 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) conducted an industrial exposure study of selected workers in two caprolactam plants, Chesterfield and Hopewell. Forty-nine workers were selected (27 smokers/ex-smokers) with 63 controls (workers not working in caprolactam areas, 42 smokers). The controls were matched to the exposed workers (all males) for age, race and smoking status. The workers selected had an average work exposure of 18.7 years (range 8.2-31.7 years) against matched controls. The level of caprolactam in the work areas was determined by industrial monitoring. The monitoring method detected total caprolactam and did not differentiate between various states of the material. The average concentrations from occasional monitoring over the previous 10 years at the Chesterfield plant averaged 4.5 mg/m^3 in the Polymer 25 area and 9.9 mg/m^3 (Spinning 26 area). Short term measurements of 15-59 minutes during specific plant operations that represented maximum short-term exposures to caprolactam ranged up to 34.8 mg/m^3. For the Hopewell plant, the levels were 4.2-7.8 mg/m^3 from occasional monitoring over 10 years, and an average of 17 mg/m^3 with a range of 2.3-30.8 mg/m^3 from short term measurements.

Pulmonary function tests were obtained by Billmaier et al. (1992) from all exposed and control workers. Pulmonary function tests began in 1978. "Nurses notes" used were from Chesterfield workers. These notes were obtained from workers who were ill, injured, had a physical examination or a return to work examination, or others over a period of 11

years. 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. However, "symptoms" recorded in the notes may not have been assessed as this was optional.

There were no significant differences between exposed workers and their controls in the pulmonary function tests or lung function over the years (Billmaier et al., 1992). Wide differences were shown in the initial (using a Collins Eagle spirometer from 1980 to 1988) and last (using a Puritan Bennet spirometer which replaced the Collins Eagle spirometer) FEV_1/FVC ratios between smokers (n=21), ex-smokers (n=12) and non-smokers (n=7) but not between smokers and controls. The authors concluded that there would be differences in the FEV_1/FVC ratios between the exposed workers and their controls if they were present.

OEHHA notes several uncertainties with Billmaier et al. (1992) that preclude it from use as the basis of a chronic REL. Difference in the FEV_1/FVC ratios in smokers, ex-smokers and non-smokers may be due to the fact that tobacco smoke is inhaled deeply whereas caprolactam may not be. Smokers could be heavy smokers, and they could smoke at work and during non-working hours; exposure to caprolactam occurs primarily at work. Other toxicological studies summarized in this document indicate the endpoint for caprolactam exposure is the upper respiratory tract. Thus, FEV_1/FVC ratios may not be an effective measure of caprolactam effects. U.S. EPA (1998) also notes that the spirometry performed was not in accordance with current guidelines and quality assurance procedures.

Another weakness is that individual worker exposure histories could not be clearly determined due to high variability in caprolactam levels and changes in job responsibilities throughout the workday. As noted earlier, the irritation data from "nurses notes" are probably unreliable and were apparently not collected systematically for all workers. Finally, the authors did not conduct a survey of the workers regarding sensory irritation symptoms or examine the upper respiratory tract for signs of inflammation.

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 chemical’s 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 inhalation 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 (P_1) rats exposed to caprolactam in feed, but were observed in the second- (P_2) and third-generation (P_3) rats treated with caprolactam (Serota et al., 1988). The P_1 rats were young adults (approximately 6 weeks old) upon initiation of treatment. Since the P_2 and P_3 animals were exposed both *in utero* and through the early growth phase, the decreased body weights noted in the P_2 and P_3 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.

Goldblatt et al., (1954) exposed three guinea pigs to 118 - 261 mg/m^3 caprolactam dust for 7 hr/day for 7 days and reported no adverse effects other than occasional cough. No other toxicological exams were apparently performed, other than observing for signs of irritation. The majority of the caprolactam particles formed for the study were below 5 µm in size.

Hohensee et al. (1951) exposed up to 10 guinea pigs to 51 mg/m^3 caprolactam 5-8 hr/day for 26-30 days. No external pathologic changes or evidence of convulsions were noted during the exposures. Pathological and histological examination of a few of the animals revealed compound-related slight inflammation of the nasal mucosa and tracheal mucosa.

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/m^3 for 6 hours/day, 5 days/week (Reinhold et al., 1998). A second group of rats was similarly exposed but

euthanized 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 and are presented in Table 3 (Reinhold et al., 1998). Male and female responses were generally similar, so the data were combined. Minimal and/or slight changes occurred in nearly all control animals indicating that as the animal ages, a low grade inflammatory change in the mucosal tissue occurs naturally in this species of rat. These are not reported in Table 3. Rather, Table 3 highlights the exacerbation by caprolactam of these naturally-occurring inflammatory changes in the rat nasal mucosa to higher grades of injury.

When low-level background changes in the nasal mucosa are excluded, a dose-related trend for increased incidence of intracytoplasmic eosinophilic material in the olfactory epithelium and goblet cell hypertrophy/hyperplasia in the respiratory epithelium was observed (Table 3). A dose-related trend for increased severity of the mucosal changes with increasing dose was also apparent, although statistical analysis of these trends were not provided by Reinhold et al. (1998). The authors considered the olfactory and respiratory mucosal changes to be exposure-related at 70 and 243 mg/m^3, but considered them to be an adaptive response to the irritant and not an adverse effect. The nasal mucosal changes were still apparent in the two highest exposure groups at the 4-week recovery sacrifice.

Unlike the nasal mucosa, no background age-related changes occurred in the larynx. With caprolactam exposure, laryngeal tissues showed a dose-related trend for increased incidence of squamous/squamoid metaplasia/hyperplasia of the pseudostratified columnar epithelium covering the ventral seromucous gland; the changes 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. The authors considered the keratinization in the larynx to be the only adverse effect observed in the upper respiratory tract of the rats, resulting in a NOAEL and LOAEL of 70 and 243 mg/m^3, respectively.

Table 3. 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	9/20	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 common in the control group and are not presented in the table.
[c] Intracytoplasmic eosinophilic material – including slight, moderate, and moderately severe changes; minimal changes were common in the control group and are not presented in the table. Only two rats of each sex showed moderately severe changes in the high exposure group.
[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 3 using benchmark dose modeling software supplied by U.S. EPA (2003). $BMCL_{05}$s (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 4. The $BMCL_{05}$ is a concentration estimated by the modeling to be the lower bound of the 5% response rate, and is used as the point of departure for REL derivation. For each endpoint, the $BMCL_{05}$ 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 $BMCL_{05}$ 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 4. $BMCL_{05}$s for the toxic endpoints in the 13-week inhalation exposure study in rats (Reinhold et al., 1998).

Endpoint	**$BMCL_{05}$ (model)**	**BMC_{05}[a] (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

[a] The BMC_{05} represents the modeled concentration resulting in a 5% response rate for the endpoint

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 5 presents the estimated range of daily caprolactam intake in feed, assuming 100% absorption, for each dose group during the study.

Table 5. Estimated range of daily intake[a] 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	207 - 397	404 - 673	263 - 370	441 - 673
Mouse	792 - 1122	2155 - 2442	1203 - 1796	3140 - 3907

[a] Caprolactam intake range for each dose group of each species was based on a week in the second year of the study with the lowest mg/kg body weight intake, and on week 4 feed consumption, the period of growth with the highest 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, Gad et al. (1987) dosed pregnant rats by gavage with caprolactam at 100, 500, or 1,000 mg/kg/day on gestation days 6-15. 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 significantly 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 embyotoxicity 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 a 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 P_2 and P_3 parental generations at 5,000 and 10,000 ppm, but body weights were unaffected in P_1 animals at all dose levels. The mean body weight changes were statistically significant ($p\leq0.05$) 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 P_2 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 ($p\leq0.05$) 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 P_1 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 P_1 animals at all dose levels, and reduced food consumption was observed only at week 10 in P_1 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, (Salamone, 1989) reported no sperm abnormality in male mice treated with 222, 333, 500, 750, or 1,125 mg/kg caprolactam by gavage daily for five days, although mortality was evident at the highest dose. Following the fifth gavage with 1,125 mg/kg caprolactam, the mice immediately became motionless. In four of the nine mice treated, this inactivity was followed 10 min later by racing around the cage and death within seconds. These deaths are probably related to the method of oral treatment because exposure of mice up to 2155 to 2442 mg/kg caprolactam in feed for two years by the NTP (1982) did not result in an increase in mortality. 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/reproductive toxicity 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 P_1 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/m^3 (697 mg/kg x 70 kg body wt. / 20 m^3/day) in a route-to-route extrapolation. Brief human exposures to lower caprolactam concentrations in the range of 1850 to 5560 mg/m^3 (400 to 1200 ppm) have been characterized as extremely irritating, and subchronic exposures of rats to air concentrations as low as 24 mg/m^3 have resulted in labored breathing and nasal secretory discharge. Applying a 100-fold uncertainty factor (10-fold UF each for interspecies and intraspecies extrapolation) for extrapolation from an animal developmental study to human exposure would produce a proposed REL of 24 mg/m^3. The acute and chronic RELs of 770 μg/m^3 and 2 μg/m^3, respectively, are considerably 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 upper respiratory tract injury occurring at lower concentrations. 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 Inhalation Reference Exposure Level (1-hour exposure)

Study	Ferguson and Wheeler, 1973
Study population	5 unacclimated adult workers
Exposure method	Exposure to industrial emission source of caprolactam vapor
Exposure duration	Several minutes
Critical effects	Nasal and throat irritation
LOAEL	10 ppm (46 mg/m^3)
NOAEL	Not observed
Time adjusted exposure	Not applied
LOAEL uncertainty factor	6
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (default: human study)
Toxicodynamic (UF_{A-d})	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	60
Acute air reference exposure level	770 µg/m^3 (170 ppb)

The only quantitative evidence for a caprolactam concentration resulting in sensory irritation in humans is from Ferguson and Wheeler (1973), in which brief exposure to 10 ppm (46 mg/m^3) resulted in nasal and throat irritation. However, OEHHA could not draw a conclusion from this study regarding a sensory irritant threshold for a caprolactam REL, as burning nostrils and throat irritation were detected at the lowest level (10 ppm; 46 mg/m^3) in unacclimated workers. Given that sensory irritation occurred in at least 4 out of 5 exposed individuals at 10 ppm, the less accurate site testing in work areas suggesting acclimated workers can tolerate slightly lower concentrations up to 7 ppm (32 mg/m^3) is not particularly persuasive for developing a sensory irritation threshold value for the general population. Thus, the authors' conclusion that 5 ppm (23 mg/m^3) is "somewhat below the no-effect level" is not adequately supported for OEHHA to propose this value as a NOAEL for sensory irritation.

No time adjustment is applied to the LOAEL since sensory irritation is generally dependent more on concentration than on time.

A default UF of 6 was applied for use of a LOAEL with respiratory symptoms of nasal and throat irritation in the absence of a NOAEL. A LOAEL to NOAEL UF = 6 was observed to be protective for 95% of mild responses (Alexeeff et al., 2002; OEHHA, 2008). Application of the LOAEL UF reduces the point of departure of 46 mg/m^3 to 8 mg/m^3. This value is just above the free-standing NOAEL for human sensory irritation observed in the caprolactam chamber exposure study by Ziegler et al. (2008).

Chemicals that have effects limited to the extrathoracic region (i.e., nose and larynx), including caprolactam, are not predicted to be greater in children compared to adults when dosimetric adjustments are made (OEHHA, 2008). Thus, no UF_{H-k} is applied for intraspecies toxicokinetic variation among individuals.

An intraspecies toxicodynamic UF_{H-d} of 10 is applied to address the potential variation in the intraspecies toxicodynamic response, including child/adult asthmatic responses to a respiratory system irritant. This UF is based, in part, on data summarized by OEHHA (2008) that shows asthmatics may be more sensitive to the effects of respiratory irritants than non-asthmatic individuals. The cumulative UF is 60 and the acute REL is 770 µg/m^3 (170 ppb).

The acute REL is supported by a human chamber exposure study by Ziegler et al. (2008), which found statistically significantly ($p<0.05$) increased subjective total symptom and complaint score at the highest concentration of 5 mg/m^3. Increasing the power of the analysis by combining all 29 subjective symptom scores resulted in a LOAEL of 5 mg/m^3 and a NOAEL of 0.5 mg/m^3. Individual objective and subjective sensory irritation scores, including eye blink, nasal resistance, and eye and nose irritation, showed an increasing trend towards irritation, but did not reach statistical significance. Thus, the highest exposure concentration of 5 mg/m^3 is a free-standing NOAEL for sensory irritation. At best, these subjective and objective findings from the study suggest that sensory irritation in healthy humans begins near 5 mg/m^3.

Study	Ziegler et al., 2008
Study population	20 human adults: 10 male, 10 female
Exposure method	Whole body chamber
Exposure duration	6 hr
Critical effects	Increased subjective total symptom and complaint score
LOAEL	5 mg/m^3
NOAEL	0.5 mg/m^3 (recommended point of departure)
Time adjusted exposure	0.5 mg/m^3 (irritant: no time adjustment applied)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (default: human study)
Toxicodynamic (UF_{A-d})	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	$\sqrt{10}$
Cumulative uncertainty factor	$\sqrt{10}$
Acute air reference exposure level	170 µg/m^3 (36 ppb)

Odor annoyance appears to be the main driver for increased total symptom score at 5 mg/m^3, although it's unclear from the study if the total score would lack statistical significance at this concentration if the odor score was removed. The ambiguity in using

the increased subjective total symptom and complaint score, in which odor annoyance appears to dominate precludes using this study as the basis of the acute REL when human sensory irritation data are available in the Ferguson and Wheeler study. Severe physiological responses to odor can be the basis of acute RELs, such as the intense nausea and headache that can be induced by exposure to hydrogen sulfide. Ziegler et al. (2008) noted that three of the 20 volunteers perceived the odor nuisance as "severe" (a score rating of 4) at 5 mg/m^3, while others did "not" feel annoyed "at all" (a score rating of 0) at this concentration. A wide variation in response to chemical odor is not unusual among human volunteers. However, the six hour exposures to caprolactam did not result in any volunteers leaving the chamber early, or appear to produce an odor response on the order of hydrogen sulfide.

We did not apply a time adjustment to the NOAEL from Zeigler et al. since sensory irritation is generally dependent more on concentration than on time. In addition, the individual and total subjective complaint scores changed little over the six hours of exposure. Chemicals that have effects limited to the extrathoracic region (i.e., nose and larynx), including caprolactam, are not predicted to be greater in children compared to adults when dosimetric adjustments are made (OEHHA, 2008). Thus, no $UF_{H\text{-}k}$ is applied for intraspecies toxicokinetic variation among individuals.

Typically, a $UF_{H\text{-}d}$ of 10 is applied to the REL derivation to address the human variation in the intraspecies toxicodynamic response to respiratory irritants, including exacerbation of asthma in children and adults. A $UF_{H\text{-}d}$ of 10 is essential for irritants such as formaldehyde, acrolein, and acetaldehyde, in which a LOAEL alone or a combined NOAEL/LOAEL have been identified for human sensory irritation. However, taking into consideration that the caprolactam LOAEL in this study is below the threshold for sensory irritation (i.e., a free-standing NOAEL for sensory irritation), and the 10-fold difference between the LOAEL and the NOAEL for an total subjective complaint endpoint that appears to be influenced mainly by mild odor annoyance, an UF of $\sqrt{10}$ rather than a 10, is sufficient to account for the toxicodynamic variation to caprolactam exposure in this instance. The resulting acute REL based on Zeigler et al. is 170 $\mu g/m^3$ (36 ppb).

This value is lower than our proposed acute REL of 170 ppb based on Ferguson and Wheeler. However, the total symptom score appears driven primarily by odor perception and not irritation. In effect, the 5 mg/m^3 is a free standing NOAEL for irritation. Thus, this study is less useful for deriving the acute REL than Ferguson and Wheeler (1973), which focused on nasal and throat irritation.

8.2 Derivation of the 8-Hour Inhalation Reference Exposure Level

Study	Reinhold et al. 1998
Study population	Sprague-Dawley CD rats (10 animals/sex/group)
Exposure method	Discontinuous whole-body inhalation exposure to 0, 24, 70, and 243 mg/m^3 caprolactam aerosol
Critical effects	Upper airway lesions of nasal and laryngeal epithelium
LOAEL	24 mg/m^3
NOAEL	Not observed
$BMCL_{05}$	3 mg/m^3
Exposure continuity	6 hours per day, 5 days/week
Exposure duration	13 weeks
Average experimental exposure	1.607 mg/m^3 (3 mg/m^3 x 6/8 x 5/7)
Human equivalent concentration	0.402 mg/m^3 (for extrathoracic respiratory effects, RGDR = 0.25
LOAEL uncertainty factor	1 ($BMCL_{05}$ used as point of departure)
Subchronic uncertainty factor	2 (for 13 wk exposure in rodents) (see below)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	60
8-Hour air reference exposure level	7 µg/m^3 (1 ppb)

The comprehensive subchronic exposure study in rats by Reinhold et al. (1998) is the basis of the 8-hour and chronic RELs. The occupational studies of long-term exposure to caprolactam were considered by OEHHA to be inadequate for use as a point of departure for 8-hour and chronic RELs (see Section 6.1 for reviews of the occupational studies).

The 8-hr REL derivation is based on a $BMCL_{05}$ = 3 mg/m^3 for a pathology grading of 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). The $BMCL_{05}$ for exacerbation of age-associated inflammatory changes to the respiratory and olfactory nasal mucosa resulted in essentially the same value (respiratory $BMCL_{05}$ = 4 mg/m^3) or was slightly greater (olfactory $BMCL_{05}$ = 12 mg/m^3).

Reinhold et al. (1998) regarded laryngeal keratinization of the metaplastic epithelium to be the primary adverse effect, resulting in a NOAEL of 70 mg/m^3. The other effects in the upper respiratory system were considered by the researchers to be normal adaptive responses to an irritant, which they did not consider a toxicological endpoint. However, OEHHA RELs include health protection against mild irritant/inflammatory effects. These types of mild inflammatory changes are primary endpoints of toxicity as indicated in the Revised Air Toxics Hot Spots Program Technical Support Document for the Derivation of

Noncancer Reference Exposure Levels and RELs for Six Chemicals (OEHHA, 2008). 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, support the lack of an observed NOAEL in the principal study.

The $BMCL_{05}$ = 3 mg/m^3 was adjusted to an average experimental exposure of 1.6 mg/m^3 for eight-hour exposures, seven days/week. The concentration at the $BMCL_{05}$ is below the saturated vapor concentration of caprolactam of 13 mg/m^3 at 25ºC. Thus, a greater proportion of caprolactam may be in gaseous form rather than the aerosol form used in the study. Although no studies have been conducted comparing the potency of gaseous or aerosol forms of caprolactam, the evidence in this document indicates both forms are expected to have the same toxicological endpoints.

Given that the predominant form humans will be exposed to at the level of the RELs will likely be the gaseous form, a regional gas dose ratio (RGDR) approach will be used for the human equivalent concentration (HEC) adjustment. The RGDR of 0.25 was calculated using US EPA methodology (OEHHA, 2008) for extrapolation from rat and human exposure. The equation for gases with respiratory effects is:

$$RGDR = (MVa/MVh) / (SAa/SAh) \qquad \text{Eq. 8-1}$$

Where:

MVa = animal minute volume
MVh = human minute volume
SAa = animal surface area for lung region of concern'
SAh = human surface area for lung region of concern

Surface areas for the region of concern, the extrathoracic region, for rat (15 cm^2) and human (200 cm^2) were obtained from Table F.1.1 in OEHHA (2008). Minute volume for rats were calculated using Eq. 8-2 below, using intercept (b_0) and slope (b_1) values from Table F.1.2 in OEHHA (2008). Body weight (BW) for both male and female rats combined (0.323 kg) was averaged over the 13-week exposure duration from body weight tables in Reinhold et al. (1998) and Hoffman (1997).

$$\log_e(MV) = b_0 + b_1 \log_e(BW) \qquad \text{Eq. 8-2}$$

Where

BW = 0.323 kg; b_0 = -0.578; b_1 = 0.821

$$\log_e(MV) = -0.578 + 0.821 \log_e(0.323 \text{ kg})$$
$$MV = 0.222 \text{ L/min or } 222 \text{ ml/min}$$

For humans, an average adult male and female combined MV of 11,944 ml/min was estimated using breathing rate data from US EPA (2009).

Thus:

RGDR = (222 ml/min/11,944 ml/min) / ($15cm^2/200\ cm^2$)
RGDR = 0.0186 / 0.075
RGDR = 0.25

A subchronic UF = 2 was incorporated into the REL derivation for extrapolation from 13-week exposure in the rats to chronic exposure. Although 13 weeks of exposure is 12.5% of the 2-year life expectancy of rats, which would entail use of a subchronic UF = 1 for >12% of lifetime exposure, U.S. EPA (1994) recommends using a subchronic adjustment factor for all 13-week studies regardless of species. OEHHA has typically used a subchronic UF = √10 for 13-week exposure studies in rats and mice. However, for rodent studies of this exposure duration a subchronic UF = 2 for upper respiratory irritants, when the resulting injury is considered mild, is appropriate.

The basis for using a subchronic UF = 2 was derived from the numerous rodent studies with formaldehyde (OEHHA, 2008). Comparison of 13-week exposure studies with studies of longer duration up to 2 years shows that the NOAELs and LOAELs for upper airway injury are often the same, with only a 2-fold difference between chronic and 13-week study NOAELs and LOAELs in some cases. The 2-fold lower NOAELs and LOAELs were often a result of the choice of the formaldehyde exposure concentration used in the studies.

The severity of the upper respiratory tract injury also supports a subchronic UF = 2. The pathology grading of the upper respiratory tract resulting from caprolactam exposure indicates only a mild increase in injury. The exacerbation by caprolactam exposure of normal nasal olfactory tissue degeneration was small, increasing from minimal to slight at the lowest dose of 24 mg/m^3. The laryngeal tissue damage caused by caprolactam was minimal, at best, at the low dose. Overall, only a few cases of moderately severe tissue injury were observed, occurring in the high concentration exposure group in olfactory tissue. In addition, all animals survived to the end of the study and the treatment-related labored breathing and nasal discharge generally decreased in incidence during the second half of the study.

We did not apply an interspecies toxicokinetic $UF_{A\text{-}k}$. 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.

We applied a default interspecies UF_{A-d} of √10 to compensate for the absence of data on pharmacodynamic differences between species. Specifically, only one comprehensive animal inhalation study in rats has been performed with caprolactam.

The toxicokinetic data for inspired upper respiratory irritants in humans suggest low interindividual variation and no dosimetry differences between adults and children (OEHHA, 2008). Thus, no UF_{H-k} is applied for intraspecies toxicokinetic variation among individuals.

While caprolactam is irritating to the upper respiratory tract, initiation or exacerbation of asthma by caprolactam has not been characterized. However, data summarized by OEHHA (2008) show asthmatics may be more sensitive to the effects of respiratory irritants than non-asthmatic individuals. Thus, an intraspecies toxicodynamic UF of 10 is applied to address the diversity in the human population, including children with asthma. Application of the cumulative UF = 60 to the human equivalent concentration of 0.402 mg/m^3 resulted in an 8-hour REL of 7 $\mu g/m^3$ (1 ppb) for caprolactam.

8.3 Derivation of the Chronic Inhalation Reference Exposure Level

Study	Reinhold et al. 1998
Study population	Sprague-Dawley CD rats (10 animals/sex/group)
Exposure method	Discontinuous whole-body inhalation exposure to 0, 24, 70, and 243 mg/m^3 caprolactam aerosol
Critical effects	Upper airway lesions of nasal and laryngeal epithelium
LOAEL	24 mg/m^3
NOAEL	Not observed
$BMCL_{05}$	3 mg/m^3
Exposure continuity	6 hours per day, 5 days/week
Exposure duration	13 weeks
Average experimental exposure	0.536 mg/m^3 (3 mg/m^3 x 6/24 hr x 5/7 days)
Human equivalent concentration	0.134 mg/m^3 (for extrathoracic respiratory effects, RGDR = 0.25
LOAEL uncertainty factor	1 ($BMCL_{05}$ used as point of departure)
Subchronic uncertainty factor	2 (for13 wk exposure in rodents)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1
Toxicodynamic (UF_{A-d})	√10 (default: no interspecies toxicodynamic data)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of contact; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (potential asthma exacerbation in children)
Cumulative uncertainty factor	60
Chronic reference exposure level	2 µg/m^3 (0.5 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 0.134 mg/m^3. The application of uncertainty factors was the same for both 8-hr and chronic RELs, resulting in a chronic REL = 2 µg/m^3 (0.5 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 greater than the level that results in severe pulmonary injury), (3) the absence of a NOAEL in the subchronic study, and (4) the lack of chronic animal inhalation exposure studies.

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