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# Acrolein

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# List of Acronyms and Abbreviations

| Acronyms and Abbreviation | Definition |
|---|---|
| AEGL | Acute Exposure Guideline Level |
| AMCV | Air monitoring comparison values |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMC | benchmark concentration |
| BMCL | benchmark concentration 95% lower confidence limit |
| C | Concentration or Celsius |
| Cal EPA | California Environmental Protection Agency |
| CFD | computational fluid dynamics |
| $CO_2$ | carbon dioxide |
| d | day or days |
| D | exposure duration, hours per day |
| DF | deposition fraction in the target region of the respiratory tract |
| DAF | dosimetric adjustment factor |
| DSD | development support document |
| E | exposure level or concentration |
| EC | effective concentration |
| ET | extrathoracic |
| ESL | Effects Screening Level |
| $^{acute}ESL$ | acute health-based Effects Screening Level for chemicals meeting minimum database requirements |
| $^{acute}ESL_{odor}$ | acute odor-based Effects Screening Level |
| $^{acute}ESL_{veg}$ | acute vegetation-based Effects Screening Level |
| $^{chronic}ESL_{nonthreshold(c)}$ | chronic health-based Effects Screening Level for linear dose response cancer effect |
| $^{chronic}ESL_{nonthreshold(nc)}$ | chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects |
| $^{chronic}ESL_{threshold(c)}$ | chronic health-based Effects Screening Level for threshold dose response cancer effects |
| $^{chronic}ESL_{threshold(nc)}$ | chronic health-based Effects Screening Level for threshold dose response noncancer effects |
| $^{chronic}ESL_{veg}$ | chronic vegetation-based Effects Screening Level |
| F | exposure frequency, days per week |
| GSH-S | glutathione *S* |
| h | hour |
| HEC | human equivalent concentration |
| HQ | hazard quotient |

| Acronyms and Abbreviation | Definition |
|---|---|
| Hg | mercury |
| HSDB | Hazardous Substances Data Bank |
| IL-1β | Interleukin 1, beta |
| IL-12 | Interleukin 12 |
| IRIS | Integrated Risk Information System |
| $g/m^3$ | gram per cubic meter |
| K | constant level or severity of response |
| Kow | octanol water partition coefficient |
| $LC_{50}$ | concentration producing lethality in 50% of experimental animals |
| LOAEL | lowest-observed-adverse-effect-level |
| LOEL | Lowest-observed-effect level |
| m | meter |
| µg | microgram |
| $\mu g/m^3$ | microgram per cubic meter |
| $mg/m^3$ | milligram per cubic meter |
| mg/L | milligram per liter |
| mm | millimeter |
| MW | molecular weight |
| min | minute |
| MOA | mode of action |
| MRL | Minimal Risk Level |
| NAC | National Advisory Committee |
| NAD+ | nicotinamide adenine dinucleotide |
| NADP+ | nicotinamide adenine dinucleotide phosphate |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| NIOSH | National Institute for Occupational Safety and Health |
| NOAEL | no-observed-adverse-effect-level |
| NOEL | no-observed-effect-level |
| NRC | National Research Council |
| OEHHA | Office of Environmental Health Hazard Assessment |
| OSHA | Occupational Safety and Health Administration |
| POD | point of departure |
| $POD_{ADJ}$ | point of departure adjusted for exposure duration |
| $POD_{HEC}$ | point of departure adjusted for human equivalent concentration |
| ppb | parts per billion |
| ppm | parts per million |
| REL | Reference Exposure Level |

| Acronyms and Abbreviation | Definition |
|---|---|
| ReV | Reference Value |
| $RD_{50}$ | exposure concentration producing a 50% respiratory rate decrease |
| RfC | Reference Concentration |
| RGDR | regional gas dose ratio |
| $(SA_{ET})_A$ | extrathoracic surface area in rats |
| $(SA_{ET})_H$ | extrathoracic surface area in humans |
| SPF OFA | SPF Sprague-Dawley OFA strain |
| T | time or exposure duration |
| TCEQ | Texas Commission on Environmental Quality |
| TD | Toxicology Division |
| TNF-α | Tumor necrosis factor-alpha |
| TWA | Time-Weighted Average |
| TWA-TLV | Time-Weighted Average Threshold Limit Value |
| UF | uncertainty factor |
| $UF_H$ | interindividual or intraspecies human uncertainty factor |
| $UF_A$ | animal to human uncertainty factor |
| $UF_{Sub}$ | subchronic to chronic exposure uncertainty factor |
| $UF_L$ | LOAEL to NOAEL uncertainty factor |
| $UF_D$ | incomplete database uncertainty factor |
| UN | United Nations |
| USEPA | United States Environmental Protection Agency |
| $(VE)_A$ | ventilation rate in animals |
| $(VE)_H$ | ventilation rate in humans |
| wk | week |

# Chapter 1 Summary Tables and Figure

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of acrolein. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (2012) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on acrolein‘s physical/chemical data. Figure 1 compares the values in Tables 1 and 2 to values developed by other federal/occupational organizations.

**Table 1 Air Monitoring Comparison Values (AMCVs) for Ambient Air**

| **Short-Term Values** | **Concentration** | **Notes** |
|---|---|---|
| acute ReV | 11 µg/m$^3$ (4.8 ppb)<br>**Short-Term Health** | **Critical Effect(s):** eye, nose, and throat irritation and decreased respiratory rate in human volunteers |
| $^{acute}ESL_{odor}$ | 8.2 µg/m$^3$ (3.6 ppb)<br>**Odor** | 50% odor detection threshold; piercing, disagreeable odor |
| $^{acute}ESL_{veg}$ | 230 µg/m$^3$ (100 ppb)<br>**Short-Term Vegetation** | Lowest-observed adverse effect level after 9 h (alfalfa leaf damage) |
| **Long-Term Values** | **Concentration** | **Notes** |
| chronic ReV (noncarcinogenic) | 2.7 µg/m$^3$ (1.2 ppb)<br>**Long-Term Health** | **Critical Effect(s):** Mild hyperplasia and lack of recovery of the respiratory epithelium in Fisher 344 rats |
| $^{chronic}ESL_{nonthreshold(c)}$<br>$^{chronic}ESL_{threshold(c)}$ | - - - | Data are inadequate for an assessment of human carcinogenic potential |
| $^{chronic}ESL_{veg}$ | - - -<br>**Long-Term Vegetation** | No data found |

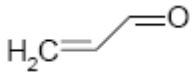
**Table 2 Air Permitting Effects Screening Levels (ESLs)**

| **Short-Term Values** | **Concentration** | **Notes** |
|---|---|---|
| $^{acute}ESL$ [1 h]<br>(HQ = 0.3) | 3.2 µg/m$^3$ (1.6 ppb) [a]<br>**Short-Term ESL for Air Permit Reviews** | **Critical Effect(s):** eye, nose, and throat irritation and decreased respiratory rate in humans |
| $^{acute}ESL_{odor}$ | 8.2 µg/m$^3$ (3.6 ppb) | 50% odor detection threshold; piercing, disagreeable odor |
| $^{acute}ESL_{veg}$ | 230 µg/m$^3$ (100 ppb) | Lowest-observed-adverse effect level after 9 h (alfalfa leaf damage) |
| **Long-Term Values** | **Concentration** | **Notes** |
| $^{chronic}ESL_{threshold(nc)}$<br>(HQ = 0.3) | 0.82 µg/m$^3$ (0.36 ppb) [b]<br>**Long-Term ESL for Air Permit Reviews** | **Critical Effect:** elevated rates of symptoms such as eye, nasal, and lower airway discomfort in humans |
| $^{chronic}ESL_{nonthreshold(c)}$<br>$^{chronic}ESL_{threshold(c)}$ | --- | Data are inadequate for an assessment of human carcinogenic potential |
| $^{chronic}ESL_{veg}$ | --- | No data found |

[a] Based on the acute ReV of 11 µg/m$^3$ (4.8 ppb) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 2.7 µg/m$^3$ (1.2 ppb) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

**Table 3 Chemical and Physical Data**

| **Parameter** | **Value** | **Reference** |
|---|---|---|
| Molecular Formula | $C_3H_4O$ | ATSDR 2007 |
| Molecular Weight | 56.1 | TCEQ 2009 |
| Chemical Structure |  | ATSDR 2007 |
| Physical State | Liquid | ATSDR 2007 |
| Color | Colorless or yellowish | ATSDR 2007 |
| Odor | Disagreeable, choking odor, pungent | ATSDR 2007 |
| CAS Registry Number | 107-02-8 | TCEQ 2009 |
| Synonyms/Trade Names | Acraldehyde, Acrylaldehyde, Acrylic aldehyde, Allyl aldehyde, Propenal, 2-Propenal, Magnicide, Magnicide H | ATSDR 2007 |
| Solubility in water | 2.12E+5 mg/L | ATSDR 2007 |
| Log $K_{ow}$ | -0.1 | TCEQ 2009 |
| Vapor Pressure | 274 mm Hg | ATSDR 2007 |
| Vapor Density (air = 1) | 1.94 | ATSDR 2007 |
| Density (water = 1) | 0.84 g/m$^3$ | ATSDR 2007 |
| Melting Point | -87.7°C | ATSDR 2007 |
| Boiling Point | 52.6°C | ATSDR 2007 |
| Conversion Factors | 1 ppm = 2.29 mg/m$^3$<br>1 mg/m$^3$ = 0.44 ppm | Toxicology Staff |

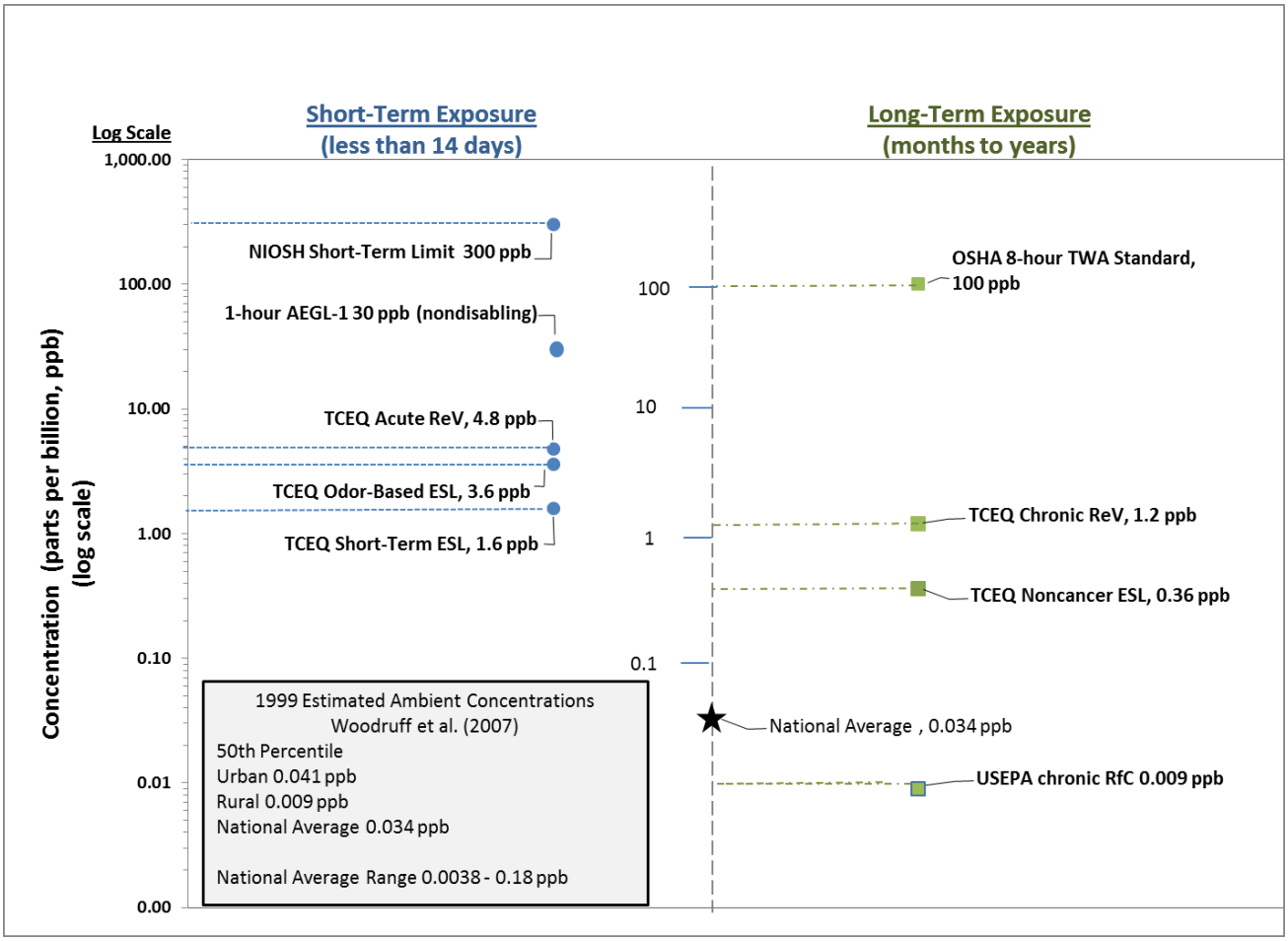



**Figure 1 Acrolein Health Effects and Regulatory Levels**

This figure compares acrolein's acute toxicity values (acute ReV, odor-based ESL, and health-based short-term ESL) and chronic toxicity values (chronic ReV and long-term ESL) found in Tables 1 and 2 to the Acute Exposure Guideline Level-1 (AEGL-1) (NRC 2009); Occupational Safety and Health Administration (OSHA) and National Institute Occupational Safety and Health (NIOSH) occupational values from NRC (2009); and to the United States Environmental Protection Agency (USEPA) Reference Concentration (RfC) (USEPA 2003).

# Chapter 2 Major Sources or Uses

According to the Hazardous Substances Data Bank (HSDB), acrolein is used as an intermediate in the production of acrylic acid, glycerine, methionine, glutaraldehyde and other organic chemicals (HSDB 2005). Acrolein is also an herbicide used for control of vegetation in irrigation canals and as a biocide in water pumped into injection wells associated with petroleum production (USEPA 2008). Humans are exposed to acrolein primarily through tobacco smoke, gasoline and diesel exhaust, structural and forest fires, and partially combusted animal fats and vegetable oils (Beauchamp et al. 1985). Seaman et al. (2007) reported that human exposure to acrolein is dominated by indoor air (3-40 times higher than concentrations measured in outdoor air) due to a combination of fixed sources (e.g., off-gassing from wood) combined with activities such as cooking.

# Chapter 3 Acute Evaluation

## *3.1 Health-Based Acute ReV and ESL*

## 3.1.1 Physical/Chemical Properties and Key Studies

### *3.1.1.1 Physical/Chemical Properties*

Acrolein is a clear or yellow liquid with a piercing, disagreeable “acrid” odor (ATSDR 2007). It is water soluble, volatile, and highly reactive. The main chemical and physical properties of acrolein are summarized in Table 3.

### *3.1.1.2 Essential Data and Key Studies*

A comprehensive literature search through December 2009 was conducted and key studies were reviewed regarding the acute toxicity of acrolein. In addition, information from both human and animal studies regarding the acute toxicity of acrolein was reviewed in detail from ATSDR (2007) and USEPA (2003), and NRC (2009). Well-conducted human studies demonstrate mild sensory irritation and respiratory effects at low concentrations and are preferentially used to develop the acute ReV and ESL. Since acrolein is reactive and very water soluble, it mainly produces sensory irritation and point-of-entry respiratory effects. Minor systemic effects are observed, but only at higher acrolein concentrations producing serious respiratory effects.

#### 3.1.1.2.1 Human Studies

Two human experimental studies with acrolein conducted by Weber-Tschopp et al. (1977) and Darley et al. (1960) were located and identified as potential key studies for the acute evaluation of acrolein.

#### *3.1.1.2.1.1 Weber-Tschopp et al. (1977)*

The key study for derivation of the ReV and ESL was conducted by Weber-Tschopp et al. (1977) which includes three separate studies and was published in German. An English translation of the article was requested and received from the ATSDR. The study authors reported the average irritation threshold for acrolein ranged from 0.09 to 0.30 ppm. Although the Weber-Tschopp et al. (1977) study was well conducted, it was somewhat difficult to ascertain the exact concentrations at which adverse effects occurred from the study's figures.

In the first sub-study, 46 healthy college students (21 males and 25 females) were exposed in groups of three for 60 minutes (min) to a constant concentration of 0.3 ppm acrolein (analytical concentration). No control exposure was discussed for this sub-study. The authors measured blink rate, respiratory rate, and subjective irritation via a question form completed by study subjects. Annoyance increased during the first 20-30 min and then remained constant throughout the remainder of the 1-hour (h) exposure period. Eye, nose, and throat irritation and blink rate increased with increased exposure time to acrolein, with eye irritation recorded as being the most sensitive. Eye irritation was described by subjects as between "a little" and "medium" irritation. The highest level of irritation occurred after about 40 min. The authors reported a significant decrease in respiratory rate after 40 min of exposure ($p<0.01$). They also reported 47 percent of subjects experienced a 10 percent decrease in respiratory rate after 10 min and 60 percent of subjects experienced a 10 percent decrease in respiratory rate after 20 min. According to the American Society for Testing and Materials (ASTM 1991 as cited in NRC 2009), a 12-20 percent decrease in respiratory rate corresponds to slight irritation and respiratory rate decreases in the range of 20 to 50 percent correspond to moderate irritation. A minimal lowest-observed-adverse-effect level (LOAEL) (i.e., an exposure level close to the expected no-observed-adverse-effect level (NOAEL)) of 0.3 ppm acrolein was identified from this sub-study based on eye, nose, and throat irritation and decreased respiratory rate.

The other sub-studies within Weber-Tschopp et al. (1977) used varying exposure concentrations and shorter exposure times. In the second sub-study, 31 male and 22 female college students were exposed for 40 min to increasing acrolein concentrations. The acrolein concentration increased in the first 35 min from 0 to 0.60 ppm and remained constant for the last 5 min. This same group of subjects served as the control group exposed under identical conditions but without acrolein exposure. Subjects filled out a question form every 5 min and blink rate was measured from two of the three subjects in each group and respiratory rate was measured continuously from the third group member. The blink rate was significantly different from control exposure at approximately 0.26 ppm ($p<0.01$). The authors reported throat irritation was found to be a less sensitive criterion than eye irritation measured via blink rate; throat irritation increased significantly at 0.43 ppm acrolein. Annoyance (measured by participant questionnaire) increased with increasing exposure; however, the answer, "wish to leave room," occurred at approximately 0.40 ppm. An approximate 25 percent decrease in respiratory rate was significantly different from that of controls at 0.6 ppm. A LOAEL of 0.26 ppm was selected from the second sub-study based on eye irritation. The third sub-study involved discontinuous

exposure to increasing concentrations of acrolein. Subjects were exposed five times for 1.5 min to either 0, 0.15, 0.30, 0.45, and 0.60 ppm. A period of recovery for 8 min occurred between each exposure. Authors stated the difference between continuous and discontinuous exposure was striking as both eye and nose irritation were stronger with continuous exposure.

#### *3.1.1.2.1.2 Darley et al. (1960)*

A study to examine eye irritation in humans resulting from exposure to ozone-hydrocarbon mixtures was conducted by Darley et al. (1960). The study's purpose was to evaluate the effects of a number of ozone-hydrocarbon mixtures; acrolein was used as the comparison chemical, as it was a known eye irritant. Approximately 31 college students (both male and female) were exposed to acrolein via only eye exposure. Each student wore an activated carbon respirator covering the mouth and nose to enable only eye exposure. Subjects were exposed to concentrations of acrolein of 0, 0.06, 1.3-1.6 ppm, or 2.0-2.3 ppm for 5 min (analytical concentrations). The subjects recorded their level of eye irritation as none (score 0), medium (score 1), or severe (score 2) every 30 seconds during the 5-min exposure.

The maximum level of eye irritation recorded by the test subjects was used as the response of that subject. The average scores of the maximum irritation scores were as follows:

| **Average of Maximum Irritation Scores** | **Concentration of Acrolein** |
|---|---|
| 0.361 | 0 ppm |
| 0.471 | 0.06 ppm |
| 1.182 | 1.3-1.6 ppm |
| 1.476 | 2.0-2.3 ppm |

At a concentration of 0.06 ppm acrolein, less than medium irritation was reported (0.471) and was similar to the irritation score resulting from exposure to filtered air alone (0.361) (i.e., slight irritation was reported during exposure to both filtered air and 0.06 ppm acrolein). Study details (including the exact number of participants, whether exposure to the ozone-hydrocarbon mixtures affected subject responses, significance of irritation scores, and whether irritation increased with exposure time) were lacking, nonetheless, the Toxicology Division (TD) identified 0.06 ppm as the NOAEL and 1.3 ppm as the LOAEL.

The Darley et al. (1960) study was not selected as the key study because the LOAEL of 1.3 ppm for eye irritation was greater than the LOAEL of 0.3 ppm for eye, nose, and throat irritation from the first substudy (Weber-Tschopp et al. 1977). The Darley et al. (1960) study also involved 5-min exposures and several study details were lacking.

The Weber-Tschopp et al. (1977) 1-h study with a LOAEL of 0.3 ppm is selected as the key study because:

- The exposure duration of 60 min corresponds to that desired for derivation of an acute ReV/ESL;
- The experimental procedures and study discussion were more robust than those of the Darley et al. (1960) study and resulted in a LOAEL similar to that from the 40-minute Weber-Tschopp et al. (1970) study; and
- Darley et al. (1960) only evaluated eye irritation for a 5-min exposure whereas the Weber-Tschopp study evaluated eye irritation (sensory effects) and effects on the respiratory tract using both qualitative and quantitative measures.

### 3.1.1.2.2 Animal Studies

Numerous acute animal studies were located involving inhalation exposure to acrolein and are discussed in ATSDR (2007) and NRC (2009). It should be noted that ATSDR (2007), noted, "Acrolein exposure levels were very comparable for the appearance of cellular changes in nasal epithelium of animals (Cassee et al. 1996b) and onset of nasal irritation in humans (Weber-Tschopp et al. 1977). Therefore, it is reasonable to extrapolate animal health effects to human health risk resulting from acrolein exposure." Studies that investigated effects in animals after exposure to acrolein at low concentrations where less serious adverse effects were noted are summarized in Table 4.

**Table 4 Summary of Acute Animal Inhalation Studies Noting Adverse Effects**

| **Study (Animal Strain)** | **Exposure Duration** | **NOAEL (ppm)** | **LOAEL (ppm)** | **Response at LOAEL** |
|---|---|---|---|---|
| Dorman et al. 2008 (Male F344 rat) | 0. 0.02, 0.06, 0.2, 0.6, 1.8 ppm<br>6 h/day (d),<br>5 d/week (wk) for up to 65 d (observations at 4, 14, 30, 65, and +60 d) | 0.2 | 0.6 | Nasal respiratory epithelial hyperplasia (4 d exposure) |
| Cassee et al. 1996b (Wistar rat) | 0, 0.25, 0.67, 1.4 ppm, 6 h/d, 1-3 d | 0.25 (6 h for 1 d) | 0.25 (6 h for 3 d) | No effects after 6 h<br>Slight effects (disarrangement of respiratory/transitional epithelium) at 0.25 ppm after 3 d. |
| Morris et al. 2003 (C57B1/6J mouse) | 0, 0.3, 1.6, 3.9 ppm<br>1 time/d, 10 min | -- | 0.3 | Decreased breathing rate, relative to mice without allergic airway disease |
| Morris et al. 2003 (C57B1/6J mouse) | 0, 1.1 ppm<br>1 time/d, 10 min | -- | 1.1 | Increased airflow resistance |
| Costa et al. 1986 (Sprague-Dawley rat) | 15, 20, 25, 30, and 80 ppm for 1 h,<br>5, 7, 9, 12 ppm for 4 h | -- | 15 for 1 h<br>5 for 4 h | Peripheral sensory irritation and toxicity at all concentrations. |
| Ballentyne et al. 1989 (Sprague-Dawley rat) | 14, 22, 24, 31, or 81 ppm for 1 h or 4.8, 7.0, 9.1, or 12.1 ppm for 4 h | | | Combined male/female $LC_{50}$ values of 26 ppm (1 h) and 8.3 ppm (4 h) (5 males/5 females/group) |
| Cassee et al. 1996a (Wistar rat) | 1.73, 11.18, or 31.90 ppm for 30 min | | 1.73<br>9.2 (6.5 to 13.7) | Decreased breathing frequency<br>$RD_{50}$ |
| Bouley et al. 1976 (as cited in NRC 2009)<br>SPF OFA rat | 0 or 0.55 ppm, 4 d, then for additional 22 d after mating | 0.55 | - | No treatment-related effects were observed on the number of pregnant rats or on the number and mean weight of fetuses. |
| Kutzman et al. 1981<br>Fischer 344 male rat | 0, 0.14, 1.4, or 4.0 ppm for 6 h/d, 5 d/wk for 62 wk | 4.0 | - | No effects on number of viable embryos, resorptions, late deaths, corpora lutea, or sperm morphology. |

#### *3.1.1.2.2.1 Dorman et al. (2008)*

One animal study (Dorman et al. 2008) was identified as a supporting study. Dorman et al. exposed adult male F344 rats whole body (n=12 rats/exposure concentration/time point) to 0, 0.02 0.06, 0.2, 0.6, or 1.8 ppm acrolein (measured concentrations were 0, 0.018, 0.052, 0.200, 0.586, and 1.733 ppm) for 6 h/d, 5 d/wk for up to 65 d. This study is appropriate to discuss in the acute section because clinical signs and histopathology were evaluated (12 rats/exposure concentration/time point) after 4 d of exposure, in addition to longer exposure periods. A NOAEL of 0.2 ppm (0/12) and a LOAEL of 0.6 ppm were identified based on the incidence of nasal respiratory epithelial hyperplasia. At 0.6 ppm, minimal nasal epithelial hyperplasia was identified in the dorsal meatus of 7/12 rats and slight/mild epithelial hyperplasia was identified in the lateral wall of 12/12 rats.

#### *3.1.1.2.2.2 Other Select Animal Studies*

Cassee et al. (1996b) exposed groups of five male rats nose-only to acrolein for 6 h/d for 1 or 3 consecutive d to 0.25, 0.67, and 1.40 ppm acrolein and reported slight nasal effects at 0.25 ppm. No treatment-related histopathological nasal lesions or cell proliferation were found after exposure to acrolein for 6 h to concentrations as high as 1.40 ppm. After 3 d exposure at 0.25 ppm, the nasal effects were mainly slight, consisting of disarrangement of the respiratory/transitional epithelium in four of five rats. One of five rats had moderate disarrangement, necrosis, thickening, and desquamation of respiratory/transitional epithelium. At the next higher exposure concentration of 0.67 ppm, three of six rats had slight, mainly disarrangement of the respiratory/transitional epithelium and three of six rats had moderate disarrangement, necrosis, thickening, and desquamation of respiratory-transitional epithelium. USEPA (2003) stated, “the nose-only exposure chamber may have delivered more dose or had a different dosimetric distribution to the nasal epithelium as compared to exposure in the whole-body chambers. In a whole body chamber, rats may bury their noses in their fur during daytime sleeping postures resulting in the animals receiving less exposure than assumed.” Because of uncertainty regarding the nose-only exposures, the 6-h NOAEL of 1.25 ppm and the 3-d LOAEL of 0.25 ppm are used only for information purposes and not used quantitatively in the calculation of an acute ReV or ESL.

Exposure to higher concentrations of acrolein (> 2 ppm) has resulted in the following observed effects in animals (ATSDR 2007):

- Lacrimation
- Decreased breathing frequency
- Severe respiratory tract irritation
- Emphysema
- Decreased body weight
- Death

More serious adverse effects (e.g., lacrimation, weakness, gasping for breath) were reported in rats and mice following exposure via inhalation to concentrations of acrolein higher than 2 ppm. Rats exposed to 12 ppm acrolein for 4 h exhibited severe eye and respiratory tract irritation, gasping, anorexia, and weakness (Murphy et al. 1964). Rats exposed to 15, 20, 25, 30, and 80 ppm acrolein for 1-h and 5, 7, 9, and 12 ppm for 4 h exhibited lacrimation, perinasal and periocular wetness, mouth breathing, decreased breathing rate, and hypoactivity (Ballantyne et al. 1989). An $RD_{50}$ (statistically derived concentration which reduces the respiratory rate by 50 percent) of 9.2 ppm was derived by Cassee et al. (1996a). The authors exposed Wistar rats for 30 min to concentrations of 1.73, 11.18, or 31.90 ppm followed by a 10 min recovery period. They reported that the rats responded with an "initial fast decreased breathing frequency" (Cassee et al. 1996a).

Two studies investigating the immunological effects of acrolein were located; USEPA (2003) states the studies suggest that acrolein exposure can inhibit pulmonary antibacterial defenses. Aranyi et al. (1986) exposed mice to a single 3-h inhalation exposure to 0.1 ppm acrolein and for 3 h/d for 5 d to 0.1 ppm acrolein to measure pulmonary bactericidal activity to inhaled *Klebsiella pneumoniae*. The single exposure caused no significant effects on streptococcal-induced mortality or bactericidal activity, but 5 d of exposure reduced bactericidal activity. Astry and Jakab (1983) found 8-h exposures to 3 and 6 ppm acrolein in mice showed a concentration-related reduction in clearance of *Staphylococcus aureus* from an 8-h pulmonary infection. Exposures to 8 to 10 ppm acrolein did not significantly add to the impairment of bactericidal activity (Astry and Jakab 1983).

#### *3.1.1.2.2.3 Developmental/Reproductive Toxicity*

Acrolein produces point-of-entry effects in the respiratory tract after inhalation exposure and significant systemic absorption does not occur (ATSDR 2007). There are no reports of reproductive or developmental toxicity following inhalation exposure to acrolein in humans (Cal EPA 2008). The World Health Organization (1992) summarized that inhalation of acrolein is unlikely to affect the developing embryo.

Two animal studies evaluating developmental/reproductive toxicity were located as shown in Table 4 and summarized by NRC (2009) below:

> SPF Sprague-Dawley, OFA strain (SPF OFA) rats were exposed to 0 or 0.55 ppm acrolein continuously for four days (Bouley et al. 1976). Three exposed males were then mated with 21 exposed females and the exposures continued for an additional 22 d, at which time the females were sacrificed. No treatment-related effects were observed on the number of pregnant rats or on the number and mean weight of the fetuses.
>
> In another study, Fischer 344 male rats were exposed to 0, 0.14, 1.4 or 4.0 ppm acrolein for 6 h/d, 5 d/wk for 62 wk (Kutzman et al. 1981).The males were then

mated with untreated females. No effects on number of viable embryos, resorptions, late deaths, corpora lutea, or sperm morphology were observed.

### 3.1.2 Mode-of-Action (MOA) Analysis

Acrolein is a highly reactive aldehyde that is strongly irritating to mucous membranes, especially the eyes and upper respiratory tract (ATSDR 2007; Beauchamp et al. 1985). As reported in USEPA (2003), "Sensory irritation and depressed breathing frequency are regarded as defense mechanisms for penetration to the lower respiratory tract." The irritant effects of acrolein may result from its reactivity toward sulfhydryl groups on receptor proteins in the nasal mucosa (Beauchamp et al. 1985). Cellular glutathione depletion has also been observed (Beauchamp et al. 1985). These adverse point-of-entry effects are assumed to have a threshold MOA. The following information was obtained from NRC (2009):

> Data regarding the metabolism of acrolein following inhalation exposure were not available; however, Patel et al. (1980) investigated the *in vitro* metabolism of acrolein in rat liver and lung preparations. Oxidation of acrolein to acrylic acid in liver 9000 g supernatant and cytosol required either NAD+ or NADP+ and was inhibited by disulfiram, suggesting the involvement of aldehyde dehydrogenase. Acrolein was also metabolized to acrylic acid when incubated with liver microsomes. In the presence of NADPH [nicotinamide adenine dinucleotide phosphate] and liver or lung microsomes, acrolein was metabolized to glycidaldehyde, a potent mutagen and carcinogen. Hydration of glycidaldehyde to glyceraldehyde was catalyzed by liver and lung epoxide hydrolase. The glycidaldehyde was also a substrate for liver and lung GSH-S transferases. Although glycidaldehyde is formed *in vitro*, there is no experimental evidence for its formation *in vivo*. Acrylic acid and glyceraldehyde can be oxidized to $CO_2$. The glyceraldehyde is metabolized to $CO_2$ by glycolytic enzymes and although the pathway of acrylic acid conversion has not been determined, it is possible that it is metabolized as a short chain fatty acid.
>
> Egle (1972) exposed anesthetized, male and female mongrel dogs to acrolein concentrations ranging from 172 to 262 ppm for 1 to 3 min. Acrolein retention by the entire respiratory tract averaged 80-85 percent of the inhaled dose and was independent of respiratory rate. Approximately 20 percent of the inhaled dose reached the lower respiratory tract. Exposure of only the lower respiratory tract resulted in retention of 65-70 percent concentration-independent retention; in this case uptake varied inversely with ventilatory rate.
>
> Many of the effects of acrolein are caused by reaction with sulfhydryl groups. Acrolein is the most toxic of the 2-alkenals (including crotonaldehyde, pentenal, and hexenal) and is also the most reactive toward sulfhydryl groups. Deactivation of the cellular protein sulfhydryl groups could result in disruption of intermediary metabolism, inhibition of cell growth or division, and cell death. The respiratory irritancy of acrolein may be due to

reactivity toward sulfhydryl groups in receptor proteins in the nasal mucosa (Beauchamp et al., 1985). Li et al. (1997) investigated the effects of acrolein on isolated human alveolar macrophage function and response *in vitro*. Acrolein induced dose-dependent cytotoxicity as evidenced by the induction of apoptosis and necrosis. At lower doses, the heme oxygenase protein was induced; however, stress protein was not induced. These data suggest that acrolein caused a dose-dependent selective induction of a stress response, apoptosis, and necrosis. Macrophage function was examined by cytokine release in response to acrolein exposure. Acrolein caused a dose-dependent inhibition of IL-1β, TNF-α, and IL-12 release.

## 3.1.3 Dose Metric

In the key and supporting studies, data on exposure concentration of the parent chemical are available. Concentration of the parent chemical is the most appropriate dose metric for the acute irritation effects of acrolein since it produces sensory irritation and point-of-entry respiratory effects.

## 3.1.4 Point of Departure (POD) for the Key Study

In the key study by Weber-Tschopp et al. (1977), humans exposed to 0.3 ppm acrolein experienced a slight, but significant decrease in respiratory rate ($p<0.01$) after 40 min of exposure. In addition, eye, nose, and throat irritation increased during exposure, with eye irritation recorded as the most sensitive parameter of irritation (eye medium irritation index), compared to irritation of the nose and throat. The relevant POD is 0.3 ppm and is considered a LOAEL.

## 3.1.5 Dosimetric Adjustments

No exposure duration adjustments were needed for the key study as human subjects were exposed for 1 h to 0.3 ppm acrolein. The appropriate human equivalent concentration POD ($POD_{HEC}$) is 0.3 ppm (LOAEL) for the critical effect.

## 3.1.6 Critical Effect and Adjustments to the $POD_{HEC}$

### *3.1.6.1 Critical Effect*

As indicated in Section 3.1.1.2.2, data suggest that eye, nose, and respiratory tract irritation is the most sensitive endpoint for short-term exposure to acrolein. The specific critical effect of acrolein exposure in the key study (Weber-Tschopp et al. 1977) is decreased respiratory rate, eye, nose, and throat irritation in humans exposed to 0.3 ppm acrolein in a one-time exposure of 60 min.

### *3.1.6.2 Uncertainty Factors (UFs)*

The MOA by which acrolein may produce toxicity is assumed to have a threshold/nonlinear MOA, as discussed in Section 3.1.2. Therefore, the $POD_{HEC}$ was divided by relevant UFs. The UF for extrapolation from animals to humans ($UF_A$) is not applicable to the key study.

The following UFs were applied to the $POD_{HEC}$ of 0.3 ppm: 10 for intrahuman variability ($UF_H$), 6.3 for extrapolation from a LOAEL to a NOAEL ($UF_L$), and 1 for database uncertainty ($UF_D$) for a total UF = 63:

- A $UF_H$ of 10 was used for intrahuman variability since the irritant effects were observed in studies involving healthy male and female college students;

- The $UF_L$ of 6.3 is consistent with the study by Alexeeff et al. (2002) which recommends the use of a $UF_L$ of 6.3 if the acute inhalation health effect is judged to be mild. The LOAEL is considered minimal due to the decreased respiratory rate of 10% which is considered slight irritation at best (i.e., 12-20 percent decrease in respiratory rate corresponds to slight irritation (ASTM 1991 as cited in NRC 2009); and

- A $UF_D$ of 1 was used because the overall database of acute toxicological studies with acrolein is large (ATSDR 2007, NRC 2009). The acute studies consist of both human and animal studies as well as short-term reproductive/developmental studies.

Key Study (Weber-Tschopp et al. 1977):

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 0.3 \text{ ppm} / (10 \times 6.3 \times 1)$$
$$= 0.00476 \text{ ppm}$$
$$= 4.76 \text{ ppb}$$

### 3.1.7 Health-Based Acute ReV and $^{acute}$ESL

The acute ReV of 4.76 ppb was rounded to two significant figures at the end of all calculations resulting in a value of 4.8 ppb. The acute ReV of 4.8 ppb (11 µg/m$^3$) was multiplied by 0.3 to calculate the $^{acute}$ESL. At the target hazard quotient of 0.3, the $^{acute}$ESL is 1.4 ppb (3.2 µg/m$^3$) (Table 5).

**Table 5 Derivation of the Acute ReV and $^{acute}$ESL**

| **Parameter** | **Summary** |
|---|---|
| Study | Weber-Tschopp et al. 1977 |
| Study population | College students; male and female |
| Study quality | High (human subjects of both genders, three sub-studies) |
| Exposure Methods | 1 h via inhalation |
| LOAEL | 0.3 ppm |
| NOAEL | None |
| Critical Effects | Eye, nose and throat irritation and decreased respiratory rate |
| PODanimal | NA |
| Exposure Duration | 1 h |
| Extrapolation to 1 h | NA |
| $POD_{ADJ}$ (extrapolated 1 h concentration) | NA |
| $POD_{HEC}$ | 0.3 ppm |
| Total Uncertainty Factors (UFs) | 63 |
| *Interspecies UF* | *NA* |
| *Intraspecies UF* | *10* |
| *LOAEL UF* | *6.3* |
| *Incomplete Database UF*<br>*Database Quality* | *1*<br>*High* |
| **acute ReV [1 h]**<br>**(HQ = 1)** | **11 µg/m3 (4.8 ppb)** |
| **acuteESL [1 h]**<br>**(HQ = 0.3)** | **3.2 µg/m3 (1.4 ppb)** |

### 3.1.8 Comparison of Acute ReV to other Acute Values

The acute ReV of 4.8 ppb is slightly higher than the acute inhalation ATSDR Minimum Risk level (MRL) for acrolein of 3 ppb. Both the TD and ATSDR used the Weber-Tschopp et al. 1977 study and a $POD_{HEC}$ of 0.3 ppm. The difference is the TD used a $UF_L$ of 6.3 whereas ATSDR used a $UF_L$ of 10. The acute ReV is also higher than the acute California Environmental Protection (Cal EPA) Reference Exposure Level (REL) of 1.1 ppb (2.5 µg/m$^3$) (Cal EPA 2008) which is based on a geometric mean of the REL values from the Darley et al. (1960) and Weber-Tschopp studies**.** In addition, as part of Cal EPA's acute evaluation, a 95% upper confidence limit on the benchmark concentration at the 5% response level ($BMCL_{05}$) of 56 µg/m$^3$ was calculated using data from the Cassee et al. (1996b) study. The resulting acute REL after time and dosimetric adjustment and applying UFs was 2.1 µg/m$^3$ (similar to their final acute REL of 2.5 µg/m$^3$.

## *3.2. Welfare-Based Acute ESLs*

### 3.2.1 Odor Perception

The Japanese Ministry of the Environment (Nagata 2003) and Katz and Talbert (1930) are approved sources of information for odor thresholds according to the TCEQ Guidelines (TCEQ 2012). In Nagata (2003), the 50% odor detection threshold for acrolein determined by the triangular odor bag method was 0.0036 ppm. Katz and Talbert (1930) reported an acrolein odor threshold of 1.8 ppm.

According to the TCEQ Guidelines (TCEQ 2012), odor detection values defined as the highest quality level of odor thresholds (Level 1) will be considered first in setting the $^{acute}ESL_{odor}$ values. The odor detection thresholds reported by Nagata (2003) was determined by the standardized methods of measuring odor and is defined as Level 1 quality data. The odor threshold reported by Katz and Talbert (1930) is defined as Level 3 quality data. Therefore, only the standardized odor detection threshold determined by Nagata (2003) was used to set the $^{acute}ESL_{odor}$. Accordingly, the $^{acute}ESL_{odor}$ for acrolein is 3.6 ppb (8.2 µg/m$^3$).

### 3.2.2 Vegetation Effects

Acrolein is used as an herbicide for control of submerged and floating aquatic weeds and algae in irrigation canals as well as irrigation reservoirs in some states (USEPA 2008). It is also used as a biocide to kill bacteria that accumulate in pipes associated with petroleum production (USEPA 2008). Acrolein is a restricted use pesticide subject to strict use limitations (e.g., sold and applied only to trained and certified applicators or persons under their direct supervision) and is not available for residential uses (USEPA 2008).

Three acute studies on the vegetative effects of acrolein in air were located and are arranged from the most serious vegetative effects to less serious or NOAEL:

- Masaru et al. (1976) exposed pollen grains of lily plants to various concentrations of gases, including acrolein, for 1, 2, or 5 h. Pollen tube lengths were measured after exposure to determine plant damage. A complete inhibition of lily pollen germination or tube elongation occurred after a 5-h exposure to 0.40 ppm acrolein in the lily seed (*Lilium longiflorum*) (Masaru et al. 1976). The serious effect level was 0.40 ppm.

- Spinach, sugar beets, endive, oats, and alfalfa plants were exposed to concentrations of acrolein of 0.1 (9 h), 0.6 (3 h), or 1.2 ppm (4.5 h) and leaves were assessed following exposure. Effects were classified as either no injury, injury typical of smog damage (production of a metallic glaze or silvering on the lower surface of leaves), and injury not typical of smog damage (Haagen-Smith et al. 1952). Alfalfa was the most sensitive plant to acrolein with leaves exhibiting marginal bleaching with numerous small necrotic spots after exposure to all three exposure levels. The lowest concentration of acrolein producing alfalfa leaf damage was 0.1 ppm; the lowest observed effect level (LOEL). No other plants were damaged after exposure to 0.1 ppm acrolein after 9 h.

- Darley et al. (1960) exposed 14-day old pinto bean plants to concentrations of 0, 0.06 ppm (calculated), 1.3-1.6 ppm, or 2.0-2.3 ppm acrolein for 70 min. Injury to the leaves was estimated the second day after exposure as percent of damage to the leaf surface. Damage was assessed on an injury scale of 0 to 10 (100 percent injury). Approximately 10 percent of the pinto bean leaf surface area damage was observed after exposure to 1.3-1.6 ppm acrolein for 70 min. The NOAEL was 0.06 ppm.

A NOAEL was noted at 0.06 ppm (pinto bean leaf damage after exposure for 70 min), whereas the LOEL of 0.1 ppm or 100 ppb (230 µg/m$^3$) (alfalfa leaf damage after exposure for 9 h) observed in the Haagen-Smith et al. (1952) study, was used to set the $^{acute}ESL_{veg}$.

## *3.3. Short-Term ESL and Values for Air Monitoring Data Evaluations*

The acute evaluation resulted in the derivation of the following values:

- acute ReV = 11 µg/m$^3$ (4.8 ppb )
- $^{acute}ESL$ = 3.2 µg/m$^3$ (1.4 ppb )
- $^{acute}ESL_{odor}$ = 8.2 µg/m$^3$ (3.6 ppb)
- $^{acute}ESL_{veg}$ = 230 µg/m$^3$ (100 ppb)

For the evaluation of ambient air monitoring data, the $^{acute}ESL_{odor}$ of 8.2 µg/m$^3$ (3.6 ppb) is lower than the acute ReV of 11 µg/m$^3$ (4.8 ppb ) and the $^{acute}ESL_{veg}$ of 230 µg/m$^3$ (100 ppb) although all values may be used for the evaluation of ambient air monitoring data (Table 1).

The short-term ESL for air permit reviews is the health-based $^{acute}ESL$ of 3.2 µg/m$^3$ (1.4 ppb) as it is lower than the $^{acute}ESL_{odor}$ and the $^{acute}ESL_{veg}$ (Table 2). The $^{acute}ESL$ (HQ = 0.3) is not used

to evaluate ambient air monitoring data.

### *3.4 Acute Inhalation Observed Adverse Effect Level*

The acute inhalation observed adverse effect level would be the LOAEL from the key human study of 300 ppb. The $LOAEL_{HEC}$ determined from human studies, where eye, nose, and throat irritation and decreased respiratory rate occurred represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same or longer durations as those used in the study. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. The inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the observed adverse effect level of 690 $\mu g/m^3$ (300 ppb) and the acute ReV of 11 $\mu g/m^3$ (4.8 ppb) (Table 5) is a factor of 62.5.

# Chapter 4 Chronic Evaluation

## *4.1 Noncarcinogenic Potential*

A comprehensive literature search through December 2009 was conducted and key studies were reviewed regarding the chronic toxicity of acrolein. In addition, information presented in the ATSDR Toxicological Profile for Acrolein (2007), California's Acrolein Reference Exposure Levels Document (Cal EPA 2008), Acute Exposure Guideline Levels (NRC 2009), and USEPA's Toxicological Review of Acrolein in support of summary information on the IRIS (2003) was evaluated. As stated previously, since acrolein is reactive and very water soluble, it mainly produces sensory irritation and point-of-entry respiratory effects.

### 4.1.1 Physical/Chemical Properties and Key Studies

For physical/chemical properties, refer to Section 3.1.1.1 and Table 3.

### 4.1.2 Key and Supporting Studies

#### *4.1.2.1 Key Study*

The key study, Dorman et al. (2008), exposed male F344 rats (whole-body exposure) to concentrations of 0, 0.02, 0.06, 0.2, 0.6, or 1.8 ppm acrolein (analytical concentrations) for 6 h/d, five d/wk for up to 65 exposure days (13 wk). Neither mortality nor a significant increase in incidence of observable clinical signs occurred following exposure to acrolein at any concentration. After 5-8 wk of exposure, the authors reported rats exposed to 0.06, 0.2, or 0.6 ppm developed significantly depressed (~3-5%) body weight gains compared to air-exposed controls after 5-8 wk of exposure. At 1.8 ppm, body weight gains were reduced by ~ 20 percent

compared to air-exposed controls. Histopathology of the respiratory tract was evaluated after 4, 14, 30, and 65 exposure days and a 60-day recovery period after the 13-wk exposure period.

Nasal respiratory epithelial hyperplasia and squamous metaplasia were more sensitive endpoints, both with a NOAEL of 0.2 ppm and a minimal LOAEL of 0.6 ppm (minimal to slight/mild hyperplasia in the dorsal meatus and the lateral wall and squamous metaplasia in the septum and the larynx). In rats exposed to $\geq$0.6 ppm acrolein, mild/moderate respiratory epithelial hyperplasia was observed following 4 or more days of exposure. As the concentration of acrolein increased, more severe effects were observed. A higher NOAEL of 0.6 ppm and a LOAEL of 1.8 ppm were identified for olfactory epithelial inflammation and atrophy. Because hyperplasia and squamous metaplasia of the respiratory epithelium were associated with exposure to acrolein at lower concentrations than olfactory epithelium atrophy, they were considered the critical effects.

Dorman et al. (2008) examined animals 60 days following cessation of acrolein exposure: At the LOAEL of 0.6 ppm for nasal respiratory epithelial hyperplasia(Table 2 of Dorman et al. 2008), hyperplasia of the lateral wall (level II) and septum (level I) did not show recovery compared to air controls as shown below in Table 6.

**Table 6 Lack of Recovery for Nasal Respiratory Epithelial Hyperplasia at the LOAEL of 0.6 ppm (number of affected/number examined)**

| **Exposure Day** | **4** | **14** | **30** | **65** | **+60 recovery** |
|---|---|---|---|---|---|
| Lateral wall (level II) | 12/12[a] (2.0)[b] | 12/12[a] (1.0)[b] | 12/12[a] (2.0)[b] | 12/12[a] (1.0)[b] | 11/12[a] (1.0)[b] |
| Septum (level I) | 0/12 | 0/12 | 0/12 | 0/12 | 10/12[a] (2)[b] |

[a] statistically significant increase in the incidence of the lesion was seen (versus air-exposed controls, $p < 0.05$, Pearson's).

[b] number in parentheses indicates average severity of the lesion seen in animals with a statistically significant lesion incidence. Unaffected animals were excluded from this calculation. 1= minimal, 2 = light/mild, 3 = moderate, 4= moderately severe.

At the LOAEL of 1.8 ppm for olfactory epithelial atrophy (Table 4 of Dorman et al. 2008), they found partial recovery of the olfactory epithelium and stated, "Areas where recovery occurred were generally the more caudal regions of the nose where lesions developed more slowly." They further state, "…subchronic exposure to relatively high levels (1.8 ppm) of acrolein inhibited

regeneration of the olfactory epithelium. It remains unknown whether the remainder of the olfactory epithelium would recover over time."

The Dorman et al. (2008) study was selected as the key study because it investigated both duration and concentration effects including several exposure groups, evaluated recovery, evaluated histopathology of the respiratory tract, and identified both a LOAEL and NOAEL. The critical effects are minimal to light/mild nasal respiratory epithelial hyperplasia in areas that did not show signs of recovery (i.e., lateral wall (level II) and septum (level I)).

#### *4.1.2.2 Supporting Studies*

Supporting studies include those by Feron et al. (1978), Kutzman et al. (1981, 1985), Costa et al. (1986), and Lyon et al. (1970). Feron et al. (1978) was determined by USEPA to be the most suitable study for the development of a reference concentration or RfC during their assessment in 2003. The Dorman et al. (2008) study was not available to USEPA for their 2003 assessment. The studies are discussed in more detail below.

Lyon et al. (1970) conducted two studies for the purposes of collecting data to derive Confined Space Guidelines for submarines. One study exposed 15 Sprague-Dawley rats, 15 guinea pigs, 9 male squirrel monkeys, and 4 male beagle dogs to acrolein concentrations of 0, 0.22, 1.0, and 1.8 ppm for 24 h/d for 90 d. All animals exposed at 0.22 ppm appeared normal. Two of four dogs exposed to 0.22 ppm had histopathological inflammatory changes in the lungs (including moderate emphysema, acute congestion, focal vacuolization of the bronchiolar epithelial cells). A LOAEL of 0.22 ppm was determined for the 90-d study (inflammatory changes in the lungs of two of four dogs). Signs of irritation (ocular and nasal discharge) in dogs and monkeys were visible from the beginning of exposure to a concentration of 1.0 ppm; although, the authors stated the signs appeared to diminish in severity as exposure continued. The authors also exposed 15 Sprague-Dawley rats, 15 guinea pigs, 2 male beagle dogs, and 9 male squirrel monkeys to 0.7 ppm or 3.7 ppm acrolein for 8 h/d, 5 d/wk for 6 wk. The lungs of animals exposed to 0.7 ppm showed chronic inflammation and occasional emphysema more prominent in dogs and monkeys. No definite alteration of the respiratory epithelium was noted. A LOAEL of 0.7 (lung inflammation) was determined for the 6-wk study. The authors stated that based on their studies, dogs and monkeys were the most susceptible of the species tested, although they stated that changes were minor in all animals continuously exposed to 0.22 ppm for 90 d.

Feron et al. (1978) conducted a 13-wk sub-chronic inhalation study (6 h/day, 5 d/wk) using groups of equal numbers of both sexes of 20 hamsters, 12 rats, and 4 rabbits per concentration using whole body exposure. Acrolein concentrations were 0, 0.4, 1.4, and 4.9 ppm. Hematological data, body weights, organ weights, and limited macroscopic and microscopic pathology were evaluated. Significantly ($p < 0.05$) decreased body weights were found after exposure to 1.4 ppm acrolein in male and female rats. Histopathological changes observed in the respiratory tract were the only effects attributed by the authors to acrolein. Rats were slightly more sensitive than the other two species to the effects of acrolein; treatment-related effects in

one rat (1/12) in the 0.4 ppm group consisting of metaplastic and inflammatory changes in the nasal cavity (reported as "slightly affected"). Conversely, hamsters and rabbits in the 0.4 ppm exposure group did not show treatment-related effects. Exposure to 4.9 ppm induced marked changes including death, severe growth retardation, increased adrenal weights, and pathological changes in the respiratory tract in all species tested. The authors stated that acrolein produces destruction and hyperplasia and metaplasia of the lining epithelium of the respiratory tract accompanied by acute and subacute inflammatory effects. A minimal LOAEL for metaplastic and inflammatory changes in the nasal cavity was 0.4 ppm; no NOAEL was identified (Feron et al. 1978). In support of the RfC for acrolein, USEPA (2003) summarized:

> "given the apparent concentration-related increase in severity of nasal lesions (i.e., slightly to severely affected), it is reasonable to consider 0.4 ppm as a minimal LOAEL (i.e., an exposure level close to the expected NOAEL). Even though only 1/12 rats at this concentration demonstrated minimal metaplastic and inflammatory changes, these effects were consistent with the pathology demonstrated at the higher concentrations in which severity was increased."

A NOAEL of 0.4 ppm and a LOAEL of 1.4 ppm based on pulmonary lesions were identified from the studies by Kutzman et al. (1981, 1985) and Costa et al. (1986). These studies involved exposure of male Fischer 344 rats (whole-body exposure) of both sexes to 0, 0.4, 1.4, or 4.0 ppm acrolein for 62 d (6 h/day, 5 d/wk). Of the approximately fifty animals in each group, 24 were assessed for pulmonary function, 8 for pathology only, 10 for cytology, and 8 for reproductive function. All examinations were done 6 d after final exposure to reduce the effect of acute exposure on results. Mortality in male rats (32 of 57) was observed in the 4.0 ppm dose group with many displaying severe acute bronchopneumonia. No female rats in the 4.0 ppm dose group died. Rats in the 0.4 ppm group did not exhibit pulmonary lesions related to acrolein exposure. Three rats in the 1.4 ppm dose group appeared to have pulmonary lesions (bronchiolar epithelial necrosis and sloughed cells lying free in the lumen) related to exposure. Nasal pathology was not examined in the Kutzman et al. (1981, 1985) studies.

Costa et al. (1986) presented the results on the lung mechanics and diffusion and associated structural correlates from the studies conducted by Kutzman et al. (1981, 1985). The authors conducted pulmonary function testing on rats 6 d after exposure ended. Rats exposed to 4.0 ppm had significant changes in tidal volume, breathing frequency, and pulmonary resistance when compared to controls and other exposure groups. Measurements of lung volume were also significantly affected in rats exposed to 4.0 ppm. Animals in the 1.4 ppm dose group did not differ functionally from controls nor show significant morphologic changes, however, there was a slight increase in collagen content. Some evidence of parenchymal restriction in the lungs was evident at 0.4 ppm, however, the authors stated, "…there were no light microscopic features that could be related to exposure."

Feron and Kruysse (1977) exposed hamsters to 0 or 4 ppm (9.2 mg/m$^3$) acrolein for 7 hr/d, 5 d/wk, for 52 wk. The authors reported neither respiratory tract tumors nor changes in other

parts of the respiratory tract following exposure. They did report inflammation, hyper-, and metaplastic changes in the nasal cavity that were reversible after a withdrawal period of about 6 mos. The chronic LOAEL for hamsters is 4 ppm; although, hamsters appear to be a less sensitive species than rats based on the study by Feron et al. (1978). The authors concluded that acrolein is irritating to the mucous membranes of the upper respiratory tract but does not possess carcinogenic activity. LeBouffant et al. (1980) exposedgroups of 20 female Sprague-Dawley rats to 0 or 8 ppm acrolein for 1 hr/d, 7 d/wk for 10 or 18 months. The study's purpose was to evaluate the effects of high doses of cigarette smoke alone or in combination with coal dust or acrolein. Occasional emphysematous areas were the only changes noted by the authors in rats exposed to acrolein for 10 or 18 months. The authors also noted, "…that the irritant effects of acrolein proved transient, as shown by the fast disappearance of the initial functional disorders."

### *4.1.2.3 Chronic Studies with Structurally-Similar Chemicals, Acrylate Esters*

Because there are few chronic studies with acrolein, a comparison with acrylate esters is presented. Acrylate esters are structurally-similar chemicals that also induce similar responses in the respiratory tract of rodents as acrolein, albeit at much higher concentrations than acrolein. Schroeter et al. (2008) and Ontario Ministry of the Environment (2009) both cite several chronic studies with acrylate esters as supporting studies for acrolein as they found no evidence of oncogenic responses after chronic exposures (Lomax et al. 1997; Reininghaus et al. 1991; Miller et al. 1985). Lomax et al. (1997) exposed rats for 24 months by inhalation to methyl methacrylate at concentrations of 0, 25, 100, or 400 ppm. No tumors were observed following chronic exposure to methyl methacrylate. Reininghaus et al. (1991) exposed rats to methyl acrylate or n-butyl acrylate at 0, 15, 45, or 135 ppm for 24 months. No oncogenic responses were observed. Miller et al (1985) also observed no tumors following a 27-month exposure to ethyl acrylate at 1, 25, or 75 ppm. Chronic studies with acrylate esters, structurally-similar chemicals to acrolein that also induce similar responses in the olfactory epithelium, show little progression in lesions

### *4.1.2.4 Reversibility and Persistence of Effects*

USEPA briefly discussed reversibility and persistence of the irritant effects of acrolein in their 2003 Toxicological Review of Acrolein. USEPA states, "Cassee et al. (1996b) does not discuss the persistence or reversibility of the observed histopathological changes in the low-dose group with exposures greater than 3 days (e.g., adaptive response). An adaptive response in nonprotein sulfhydryl levels after 3 days of exposure was observed and is discussed. It is possible that an adaptative response to the irritant effects of acrolein occurs over time. Conversely, cessation of exposure for 2 days each week in the Feron et al. (1978) study might have provided a period during which partial recovery from nasal effects could occur. Because the Feron et al. (1978) study was much longer in duration, it is possible that some adaptation to the irritant effects of acrolein occurs with increasing duration, or that cessation of exposure for 2 days each week provides a period during which partial recovery from nasal effects might have occurred."

#### *4.1.2.5 Summary of Key and Supporting Studies*

The observed effects and LOAEL/NOAELs that were noted in these subchronic studies were very similar to each other:

- Lyon et al. (1970): a LOAEL 0.22 ppm (histopathological inflammatory changes in dogs and monkeys);
- Feron et al. (1978): a LOAEL of 0.4 ppm (metaplastic and inflammatory changes in the nasal cavity of 1/12 rats)
- Kutzman et al. (1985): a NOAEL of 0.4 ppm and LOAEL of 1.4 ppm (exposure related lesions in rats)
- Dorman et al. (2008): a NOAEL of 0.2 ppm and LOAEL of 0.4 ppm (respiratory epithelial hyperplasia in rats).

Acute effects observed in animals exposed to acrolein occur at similar concentrations (Table 4) as effects that are observed after subchronic exposure. The findings from Dorman et al. (2008) in Appendix A and comparison of concentrations producing acute and chronic effects indicate that concentration plays more of a role in the nasal and respiratory irritant effects of acrolein than duration of exposure.

### 4.1.3 Mode-of-Action (MOA) and Dose Metric

Refer to Section 3.1.2 for a discussion of the MOA for acrolein. As stated in USEPA (2003), "acrolein is highly reactive and can induce toxicity in a variety of ways. An increase in reactive oxygen species resulting from reaction with and depletion of glutathione is considered to be the primary mechanism of toxicity (Zitting and Heinonen, 1980; Arumugam et al., 1999a). Reactions with cell membrane proteins and inhibition of regulatory proteins may also play a role." As a result of acrolein's high degree of reactivity during inhalation, deposition occurs primarily in the nasal mucosa with the accompanying pathological effects. As concentrations increase, penetration and toxicity occur deeper within the respiratory system. Effects in other organs such as the liver were occasionally reported (Lyon et al., 1970), but only at concentrations higher than those affecting the respiratory system and the mechanism(s) for the effects are uncertain given acrolein's high reactivity.

For the critical effects that were not reversible for nasal respiratory epithelial hyperplasia (Dorman et al. 2008), exposure concentration of the parent chemical are available. Since data on other more specific dose metrics are not available, the exposure concentration of the parent chemical was used as the default dose metric. Schroeter et al. (2008) used the data from Dorman et al. (2008) to develop a tissue dose-based NOAEL for acrolein. In Shroeter et al. (2008), a human nasal computational fluid dynamics (CFD) model was used to extrapolate adverse effects in rats from Dorman et al. (2008) to humans using tissue dose and responses. However, the

modeling was done using a NOAEL of 0.6 ppm based on olfactory epithelial atrophy, instead of the more relevant NOAEL of 0.2 ppm based on respiratory hyperplasia. Therefore, the Schroeter et al. (2008) study and tissue dose-based dose-metric were not used in determining dosimetric adjustments for acrolein.

## 4.1.4 POD for Key Study

The POD identified from the key study was the NOAEL of 0.2 ppm for nonreversible hyperplasia of nasal respiratory epithelial (Dorman et al. 2008). These effects were not amenable to benchmark dose modeling because incidences were either 0% at lower concentrations or 100% at the LOAEL and above.

## 4.1.5 Dosimetric Adjustments

### *4.1.5.1 Exposure Duration Adjustments*

Rats were exposed for 6 h/day, 5 d/wk, thus the following calculation will be applied to adjust the discontinuous exposure to a continuous exposure to obtain an adjusted NOAEL:

$$POD_{ADJ} = POD \times D/24\ h \times F/7\ d$$

Where:

$POD_{ADJ}$ = POD from animal studies, adjusted to continuous exposure scenario

POD = POD from animal studies, based on discontinuous exposure scenario

D = exposure duration, h per day

F = exposure frequency, days per wk

$$POD_{ADJ} = 0.2\ ppm \times 6\ h/24\ h \times 5d/7d$$

$$POD_{ADJ} = 0.03571\ ppm$$

### *4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure*

Acrolein is soluble in water and highly reactive. The health effects produced by acrolein at lower concentrations are respiratory tract effects in the extrathoracic region of the respiratory tract, so dosimetric adjustments were performed as a Category 1 vapor based on updated recommendations in USEPA (2012) in order to calculate a $POD_{HEC}$. A default value of 1 was used for the Regional Gas Dose Ratio (RGDR) for a Category 1 gas with extrathoracic respiratory effects (USEPA 2012).

For Category 1 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$$

$$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$$

$$= 0.03571 \text{ ppm} \times 1$$

$$= 0.03571 \text{ ppm or } 35.71 \text{ ppb}$$

### 4.1.6 Adjustments of the $POD_{HEC}$

Acrolein acts as a sensory and upper respiratory tract irritant and both of these effects are assumed to have a threshold. Therefore, UFs were applied to the $POD_{HEC}$ to derive a ReV (i.e., assume a threshold MOA).

- The $UF_H$ of 10 was applied to account for human variability and sensitive subpopulations to the effects of acrolein. Some evidences exists to suggest that acrolein exacerbates asthma in adults and children (Cal EPA 2008).

- The $UF_A$ of 3 was used for animal-to-human extrapolation. The RGDR for a Category 1 gas was calculated using study-specific body weight data (Dorman et al. 2008) and applied to the $POD_{ADJ}$ to account for toxicokinetic differences between the rat and humans. Only the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty. The $UF_A$ is conservative because the rat is an obligatory nose-breather, in contrast to humans (Nemec et al. 2008). According to Nemec et al. (2008), "studies have found clear species-specific differences, particularly between rats and humans, suggesting that rats are often much more sensitive to localized nasal insult from inhaled toxicants (Morgan and Monicello 1990; Kimbell et al. 1997; Frederick et al. 2002)."

- A $UF_{Sub}$ of 1 rather than 10 was applied for adjustment from sub-chronic to chronic duration because:

    - there is a very close agreement of both NOAELs and LOAELs from acute and subchronic animal and human studies;

    - effects observed after 4 d of exposure were similar to effects occurring after 14, 30, and 65 d of exposure in the Dorman et al. 2008 study (Appendix A) indicating concentration was generally more important in producing adverse effects than duration of exposure; and

- chronic studies with acrylate esters, structurally-similar chemicals that induce similar responses in the olfactory epithelium, show little progression in lesions (Schroeter et al. 2008, Ontario Ministry of the Environment 2009).

- The $UF_D$ of 1 was used because the database for acrolein was considered complete and of high quality.

- The $UF_L$ was not applicable as the POD was a NOAEL

A total UF of 30 was applied to the $POD_{HEC}$ of 35.71 ppb.

$$\text{Chronic ReV} = POD_{HEC}/(UF_H \times UF_A \times UF_{Sub})$$

$$= 35.71 \text{ ppb} /(10 \times 3 \times 1)$$

$$= 35.71 \text{ ppb}/(30)$$

$$= 1.190 \text{ ppb}$$

### 4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

The chronic ReV of 1.190 ppb was rounded to two significant figures at the end of all calculations resulting in a value of 1.2 ppb (2.7 µg/m$^3$). The rounded chronic ReV was then multiplied by 0.3 to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 0.36 ppb (0.82 µg/m$^3$) (Table 7).

**Table 7 Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$**

| **Parameter** | **Summary** |
|---|---|
| Study | Dorman et al. 2008 |
| Study Population | 360 adult Fischer-344 rats (12 rats/exposure concentration/time point) |
| Study Quality | High |
| Exposure Method | Discontinuous whole body at 0, 0.018, 0.052, 0.20, 0.586, or 1.733 ppm |
| Critical Effects | Mild hyperplasia and lack of recovery of the respiratory epithelium |
| Exposure Duration | 6 h/day, 5 d/wk for 13 wk (65 d) |
| LOAEL | 0.6 ppm |
| NOAEL | 0.2 ppm |
| $POD_{ADJ}$ | 0.03571 ppm |
| $POD_{HEC}$ | 0.03571 ppm ($RGDR_{ET}$ = 1) |
| Total UFs | 30 |
| *Interspecies UF* | 3 |
| *Intraspecies UF* | 10 |
| *LOAEL UF* | NA |
| *Subchronic to chronic UF* | 1 |
| *Incomplete Database UF* | 1 |
| *Database Quality* | High |
| **chronic ReV (HQ = 1)** | **2.7 µg/m3 (1.2 ppb)** |
| **$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)** | **0.82 µg/m3 (0.36 ppb)** |

## 4.1.8 Comparison of the Chronic ReV to other Chronic Values

Table 8 presents a comparison of the chronic ReV to the RfC developed by USEPA (2003) and the REL developed by Cal EPA (2008).

**Table 8 Comparison of the Chronic ReV to Other Chronic Values**

| **Agency (Study)** | **POD** | **$POD_{ADJ}$** | **$POD_{HEC}$** | **Total UFs** | **Values** |
|---|---|---|---|---|---|
| TCEQ ReV (Dorman et al. 2008) | 0.2 ppm (NOAEL) | 0.03571 ppm | 0.03571 ppm [a] | 30 | 1.2 ppb |
| USEPA RfC (Feron et al. 1978) | 0.4 ppm (LOAEL) | 0.0070 ppm | 0.008723 ppm [b] | 1000 | 0.0087 ppb |
| Cal EPA REL (Dorman et al. 2008) | 0.2 ppm (NOAEL) | 0.036 ppm | 0.03 ppm [c] | 200 | 0.15 ppb |

[a] dosimetric adjustments using the $RGDR_{ET}$ = 1 (USEPA 2012)

[b] dosimetric adjustments using the RGDR with default body weight (USEPA 1994)

[c] dosimetric adjustment factor of 0.85 based on modeling done by Kimbell et al. (2001) with formaldehyde.

### *4.1.8.1 USEPA*

USEPA's 2003 RfC of 0.02 µg/m3 (0.0087 ppb) is based on the study by Feron et al. (1978) with a LOAEL of 0.4 ppm, dosimetric adjustments using the RGDR (USEPA 1994) with default body weight, and a cumulative UF of 1000.

### *4.1.8.2 Cal EPA*

The REL developed by Cal EPA is 0.35 µg/m³ (0.15 ppb) (Cal EPA 2008). Their chronic REL is based on the Dorman et al. (2008) study with a NOAEL of 0.2 ppm (lesions in respiratory epithelium) and a cumulative UF of 200. Cal EPA also applied a dosimetric adjustment factor (DAF) of 0.85 based on comparative modeling of gas flux in human and rat nasal passages with formaldehyde to calculate a $POD_{HEC}$ of 0.03 ppm. The TD did not find that method preferable in deriving the ReV for acrolein.

In deriving their REL for acrolein, Cal EPA (2008) derived a dosimetric adjustment factor or DAF based on modeling done by Kimbell et al. (2001) with formaldehyde. Kimbell et al. (2001) used a computational fluid dynamics (CFD) model to estimate mass flux of formaldehyde across 20 consecutive bins that represented the nasal passages. In applying the DAF to acrolein, it was assumed that acrolein and formaldehyde deposit similarly in the nasal passages (Cal EPA 2008). In an email communication with Dr. Schroeter (2009), he stated that the nasal dosimetry patterns for acrolein and formaldehyde are quite different. Cal EPA also applied a UF of 2 to account for the toxicokinetic uncertainty, as they used modeling with formaldehyde and applied it to acrolein. Because of the additional uncertainty in applying data from formaldehyde to acrolein,

the Kimbell et al. (2001) model results were not used in the TD's derivation of the $POD_{HEC}$ for acrolein. Instead,the TD used updated recommendations from USEPA (2012) for dosimetric adjustments using the $RGDR_{ET}$ = 1, although there were other studies and approaches reviewed by the TD as discussed below.

#### *4.1.8.3 Schroeter et al. (2008)*

As mentioned previously, Schroeter et al. (2008) used the data from Dorman et al. (2008) to develop a tissue dose-based NOAEL for acrolein. In Shroeter et al. (2008), a human nasal CFD model was used to extrapolate adverse effects in rats from Dorman et al. (2008) to humans using tissue dose and responses. However, the modeling was done using a NOAEL of 0.6 ppm and a LOAEL of 1.8 ppm for olfactory neuronal loss instead of the more relevant NOAEL of 0.2 ppm based on respiratory hyperplasia. Therefore, the Schroeter et al. (2008) study was not used specifically in determining dosimetric adjustments for acrolein. In an email communication with Dr. Schroeter (2009), he stated that although he did not report a dosimetric adjustment factor in his paper for the extrathoracic region, it nonetheless would be very similar to the $RGDR_{ET}$ of 0.14. This may be entirely coincidental as his estimate was based on interspecies differences in olfactory dosimetry. The RfC developed by Schroeter was 0.27 ppb ($POD_{HEC}$ = 8 ppb divided by total UFs of 30).

#### *4.1.8.4 ATSDR*

ATSDR did not derive a chronic-duration MRL for inhalation of acrolein in 2007 due to an inadequate database.

### *4.2 Carcinogenic Potential*

Chronic human or animal inhalation or oral studies indicating that acrolein has carcinogenic potential are not available, so a chronic carcinogenic value was not developed. As stated in the summary of acrolein data in IRIS (USEPA 2003),

> "Under the Draft Revised Guidelines for Carcinogen Risk Assessment (EPA 1999), the potential carcinogenicity of acrolein cannot be determined because the existing 'data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure.'
>
> There are no adequate human studies of the carcinogenic potential of acrolein. Collectively, experimental studies provide inadequate evidence that acrolein causes cancer in laboratory animals. Specifically, two inhalation bioassays in laboratory animals are inadequate to make a determination because of protocol limitations. Two gavage bioassays failed to show an acrolein-induced tumor response in two species of laboratory animals. Suggestive evidence of an extra-thoracic tumorigenic response in a drinking water study in female rats was not supported in the reanalysis of data by an independently-convened pathology working group. Questions were also raised about the

> accuracy of the reported levels of acrolein in the drinking water from this study. A skin tumor initiation-promotion study was negative, and the findings from an intraperitoneal injection study were of uncertain significance. Although acrolein has been shown to be capable of inducing sister chromatid exchange, DNA cross-linking and mutations under certain conditions, its highly reactive nature and the lack of tumor induction at portals of entry make it unlikely that acrolein reaches systemic sites at biologically-significant exposure levels. The observations of positive mutagenic results in bacterial systems occurred at high concentrations near the lethal dose."

### 4.2.1 *In vitro* Mutagenicity

The ATSDR summarized the *in vitro* mutagenicity of acrolein in their 2007 Toxicological Profile for Acrolein. In it, the ATSDR stated,

> "The overall evidence indicates that acrolein is weakly mutagenic without activating systems and non-mutagenic in the presence of activating systems in *Salmonella typhimurium* (Andersen et al. 1972; Bartsch et al. 1980; Basu and Marnett 1984; Bignami et al. 1977; Eder et al. 1982; Florin et al. 1980; Foiles et al. 1989; Khudoley et al. 1987; Lijinsky and Andrews 1980; Loquet et al. 1981; Lutz et al. 1982; Marnett et al. 1985; Parent et al. 1996b; Waegemaekers and Bensink 1984) and *Escherichia coli* (Bilimoria 1975; Ellenberger and Mohn 1977; Hemminki et al. 1980; Parent et al. 1996b; VanderVeen et al. 2001; Von der Hude et al. 1988). In the yeast, *Saccharomyces cerevisiae*, acrolein was not mutagenic without activating systems (Izard 1973). In mammalian cells, acrolein gave positive results without activating systems (Au et al. 1980; Moule et al. 1971; Munsch et al. 1973, 1974). Acrolein inhibited the activity of DNA polymerase as well as DNA and RNA synthesis in rat liver cell nuclei (Crook et al. 1986a; Curren et al. 1988; Grafstrom et al. 1988; Krokan et al. 1985). The inconsistencies in the *in vitro* assay results may be due, in part, to the high cytotoxicity of acrolein to these systems."

### 4.2.2 In vivo Mutagenicity

No data were found regarding *in vivo* mutagenicity of acrolein.

## *4.3 Welfare-Based Chronic ESL*

No data were found regarding long-term vegetative effects.

## *4.4 Long-Term ESL and Values for Air Monitoring Data Evaluations*

The chronic evaluation resulted in the derivation of the following values:

- Chronic ReV = 2.7 $\mu g/m^3$ (1.2 ppb)
- ${}^{chronic}ESL_{threshold(nc)}$= 0.82 µg/m3 (0.36 ppb)

The chronic ReV of 2.7 µg/m$^3$ (1.2 ppb) is used for the evaluation of ambient air monitoring data (Table 1). The long-term ESL for air permit reviews is the health-based $^{chronic}ESL_{threshold(nc)}$ of 0.82 µg/m$^3$ (0.36 ppb) (Table 2). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

## *4.5 Chronic Observed Adverse Effect Level*

The LOAEL value of 0.6 ppm determined in a rat 13-wk study (Dorman et al. 2008) (Table 7) was used as the POD for calculation of a chronic inhalation observed adverse effect level. No duration adjustment was made (TCEQ 2012). However, an animal-to-human dosimetric adjustment was made to calculate a $LOAEL_{HEC}$:

The $LOAEL_{HEC}$ was calculated using the following equation:

$$LOAEL_{HEC} = LOAEL \times RGDR_{ET} \text{ (Section 4.1.5.2)}$$

$$= 0.6 \text{ ppm} \times 1$$

$$= 0.6 \text{ ppm or } 6{,}000 \text{ ppb}$$

The $LOAEL_{HEC}$ determined from an animal study, where effects occurred in some animals, represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. The chronic inhalation observed adverse effect level of 14,000 µg/m$^3$ (6,000 ppb) is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the chronic inhalation observed adverse effect level of 6,000 ppb to the ReV of 1.2 ppb is a factor of approximately 5,000.

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# Appendix A Incidence Data from Dorman et al. (2008)

Table A-1 Incidence (number affected/number examined) of Epithelial Squamous Metaplasia (Dorman et al. 2008)

| **Acrolein Concentration (ppm)** | | **Air** | | | | | **0.2 ppm** | | | | | **0.6 ppm** | | | | | **1.8 ppm** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Exposure Day | | 4 | 14 | 30 | 65 | +60 | 4 | 14 | 30 | 65 | +60 | 4 | 14 | 30 | 65 | +60 | 4 | 14 | 30 | 65 | +60 |
| Nasal respiratory | Level | | | | | | | | | | | | | | | | | | | | |
| Dorsal meatus | I | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 1/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 11/11 (1.5) | 12/12 (1.3) | 11/12 (1.0) | 12/12 (1.3) | 6/12 (1.0) |
| Lateral wall | II | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 1/12 | 0/12 | 0/12 | 0/12 | 0/12 | 11/11 (2.9) | 12/12 (3.0) | 12/12 (2.6) | 12/12 (2.8) | 0/12 |
| | III | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 10/11 (1.2) | 12/12 (1.1) | 12/12 (1.9) | 12/12 (1.5) | 0/12 |
| Septum | I | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 7/12 (1.0) | 9/12 (1.0) | 6/12 (1.0) | 10/12 (1.0) | 2/12 | 11/11 (1.8) | 11/12 (1.0) | 11/12 (1.0) | 12/12 (1.0) | 8/12 (1.8) |
| | II | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 7/11 (1.0) | 12/12 (1.0) | 12/12 (1.0) | 11/12 (1.0) | 0/12 |
| | III | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 10/11 (1.1) | 12/12 (1.0) | 12/12 (1.8) | 9/12 (1.1) | 0/12 |
| Maxillo-turbinate | I | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 2/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 9/11 (1.1) | 6/12 (1.0) | 10/12 (1.0) | 10/12 (1.1) | 6/12 (1.0) |
| | II | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 9/11 (1.0) | 11/12 (1.0) | 10/12 (1.6) | 12/12 (2.5) | 0/12 |
| Nasopharyn-geal duct | V | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 12/12 (1.1) | 10/12 (1.0) | 4/12 (1.0) | 0/12 | 0/12 |

| **Acrolein Concentration (ppm)** | | **Air** | | | | | **0.2 ppm** | | | | | **0.6 ppm** | | | | | **1.8 ppm** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Exposure Day** | | **4** | **14** | **30** | **65** | **+60** | **4** | **14** | **30** | **65** | **+60** | **4** | **14** | **30** | **65** | **+60** | **4** | **14** | **30** | **65** | **+60** |
| **Nasal olfactory** | **Level** | | | | | | | | | | | | | | | | | | | | |
| **Dorsal meatus** | **II** | 0/12 | 0/12 | 0/12 | 1/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | **11/11** (2.0) | **11/12** (1.0) | **12/12** (1.1) | **12/12** (1.1) | 0/12 |
| | **III** | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | **12/12** (1.0) | **12/12** (1.0) | **8/12** (1.1) |
| **Ethmoid turbinate** | **III** | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 2/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 1/11 | **7/12** (1.0) | **12/12** (1.5) | **12/12** (1.5) | 0/12 |
| **Larynx** | | 0/12 | 0/12 | 1/12 | 5/12[c] | 7/12 | 0/12 | 1/12[b] | 1/12 | 6/12[c] | 6/12 | 2/12 | **5/12** (1.0) | **6/12** (1.5) | 7/12[c] | 7/12 | **12/12** (2.0) | **9/12** (1.9) | **12/12** (1.7) | **12/12**[c] (1.7) | **10/12** (1.4) |
| **Trachea** | | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | 0/12 | **12/12** (1.0) | **11/12** (1.0) | 0/12 | 0/12 | 0/12 |

Bold numbers denote that a statistically significant increase in the incidence of the lesion was seen (vs. air-exposed controls, $p < .05$, Pearson's).

[a] Number in parentheses indicates average severity of the lesion seen in animals with a statistically significant lesion incidence. Unaffected animals were excluded from this calculation. 1= minimal, 2 = light/mild, 3 = moderate, 4= moderately severe.

[b] Lesion incidence at 0.02 ppm = 1/12 (mild) and at 0.06 ppm = 4/12 ($p < 0.05$, average severity score of affected animals = 1.0).

[c] Larynx squamous epithelial metaplasia data at 65 d exposure used in BMD modeling.