MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 11, 2008

TO: Catherine Simon, Supervisor, Toxics Unit, Air Quality Division

FROM: Robert Sills, Toxicologist Specialist, Air Quality Division

SUBJECT: ITSLs for Acrolein (CAS #107-02-8)

As we have discussed, it is appropriate to update and re-evaluate the current ITSLs for acrolein. This memorandum pertains to a recommended change in the ITSL for acrolein. It describes the methodology chosen as the most appropriate, based on toxicological grounds, supported by the scientific data. As with the previous ITSL change (February 11, 2000 memo), the chosen approach deviates from Rule 229(2)(a) which prescribes the use of the methodology in Rule 232. Therefore, this approach requires approval, as specified in Rule 229(2)(b). I am requesting you to grant that approval on the basis of the justification that follows.

Currently, the ITSLs for acrolein are an annual AT ITSL of 0.02 micrograms per cubic meter (ug/m^3), based on the U.S. Environmental Protection Agency (EPA) Reference Concentration (RfC), and additionally an acute ITSL for protection against short-term adverse effects at a concentration of 0.5 ug/m^3 with a one-hour AT.

The following ITSL values are recommended:
Acute ITSL = 5 ug/m^3 (1 hr AT)
Chronic ITSL = 0.02 ug/m^3 (annual AT) (no change)

Literature Update:

The toxicological literature review update for acrolein via CAS-online and the NLM database was conducted on January 7, 2008. This update covered the period since the previous update on March 30, 2004. Updated risk assessments from the ATSDR and Cal-OEHHA were obtained and reviewed. The EPA IRIS database was also reviewed; it was last updated in 2003. The status of the AEGL was also reviewed.

The updated review of the primary toxicological literature did not reveal any additional key information affecting the acrolein risk assessment (acute or chronic). However, the review of recent risk assessments by other reputable agencies/committees provided valuable insights to the interpretation and application of the key study findings in risk assessment.

I. Acute noncancer risk assessment

A. Summary of the Key Studies of Acute Effects:

Available review documents (EPA, 1986, 2003a, 2003b; ATSDR, 1990, 2007; Cal EPA OEHHA, 2007a; NAC/AEGL, 1998) describe a number of studies of acute human exposure to airborne acrolein. These studies indicate the propensity of acrolein to be extremely irritating to the upper respiratory tract and eyes. Many reported findings involve relatively high exposure concentrations and short exposure periods. The better studies, with good study documentation and relatively lower levels of exposure, are summarized below. Because good-quality key studies of acute airborne exposure to acrolein in humans are available, the available animal studies are not summarized herein for the sake of brevity, but are summarized in the review documents cited above.

A key study by Weber-Tschopp et al. (1977) is published in German with an abstract in English. This paper has been translated and discussed in detail by the NAC/AEGL (2004a, 2004b, 1998), ATSDR (2007), and EPA (2003b). Additionally, DEQ staff (Chris Hull) provided translations of some key sections. In this clinical study, three experiments were performed using male and female student volunteers in climatic chambers: (1) a continuous exposure at constantly increasing acrolein concentrations, (2) short exposures to successively increasing concentrations, and (3) a 1-hour exposure to a constant concentration. In experiment (1), 31 males and 22 females were exposed to acrolein for 40 minutes during which the concentration was gradually increased to 0.6 ppm (1.4 mg/m^3) during the first 35 minutes, then remained constant. The standard deviation in the acrolein concentration was 0.023 ppm (3.8%), indicating that the actual concentrations closely matched the nominal levels. Groups of unexposed students were used as controls. The subjects had to fill out a questionnaire for the first 5 minutes. After that, the eye blinking frequency of two subjects was measured as well as the breathing frequency of a third subject during the entire exposure. The incidence (not specified) of complaints about eye irritation was reportedly significantly higher ($p<0.01$) than controls beginning at 0.09 ppm (0.21 mg/m^3) at about 5 minutes, and was increasing even at 0.6 ppm (1.4 mg/m^3). Nasal irritation was significantly higher ($p<0.01$) than controls beginning at 0.26 ppm (0.6 mg/m^3) and was increasing even at 0.6 ppm (1.4 mg/m^3). Throat irritation increased significantly at 0.43 ppm (1 mg/m^3). The eye blink frequency increased significantly beginning at 0.26 ppm (0.6 mg/m^3) ($p<0.01$).

In experiment (2), 17 males and 25 females were exposed in groups of 5, for 1.5 minutes to successive concentrations of 0, 0.15, 0.3, 0.45, and 0.6 ppm (0, 0.3, 0.7, 1.0, and 1.4 mg/m^3). After one minute of exposure they were administered a questionnaire. Between each exposure they were allowed to recuperate in a clean room for 8 minutes. As in the first experiment, eye blink frequency and respiration rate were measured. The same controls as for the first experiment were used. Eye and nasal irritation were significantly higher ($p<0.05$) than controls beginning at 0.3 and 0.6 ppm (0.7 and 1.4 mg/m^3), respectively. Throat irritation was not evident.

In experiment (3), 21 males and 25 females were exposed for 60 minutes to a constant acrolein concentration of 0.3 ppm (0.7 mg/m^3). As in the other two experiments, eye

blink frequency and respiration rate were measured. In controls, measurements of eye blink and breathing frequency, and subjective symptoms of irritation were assessed at the beginning of exposure. Each of the effects increased significantly ($p<0.01$) during the first 20-30 minutes of exposure compared to controls, after which the irritation effects reached a plateau. Eye blink frequency reached a steady state rate after 10 minutes of exposure. During exposure there was a decrease in the average respiration rate (in 16 individuals) after 40 minutes ($p<0.01$). The degree of reduction of the respiratory rate (statistically significant over the final 20 minutes) was an average reduction of 20 percent. Each individual that demonstrated an increase in eye blink frequency also reported a sharp increase in eye irritation. Throat irritation, not a significant response in the previous two experiments, was increased compared to controls after 10 minutes of exposure.

It was concluded by Weber-Tschopp et al. (1977) that the average threshold of sensation lies in the range of 0.09 (eye irritation) to 0.30 ppm (respiration rate, throat irritation). The English abstract of the Weber-Tschopp et al. (1977) study states that the effects were significant at 0.09 ppm and higher. Therefore, the reported LOAEL was 0.09 ppm; this appeared at approximately 5" into the exposure period. Nasal irritation reportedly began at 0.15 ppm (0.34 mg/m^3) but was first statistically significant at 0.26 ppm (0.6 mg/m^3). Statistically significant increased blinking rate occurred at 0.26 ppm (0.60 mg/m^3, but the effect was first noted as increased at 0.17 ppm (0.39 mg/m^3)); throat irritation began at 0.43 ppm (0.99 mg/m^3); and the respiratory rate was statistically significantly decreased at 0.6 ppm (1.38 mg/m^3). This interpretation of the results is consistent with that of EPA (2003b) and NAC/AEGL (2004a, 2004b, 1998). It should be noted that the ATSDR (1990) translation and interpretation of this study concluded that the eye irritation LOAEL was 0.17 ppm (0.39 mg/m^3) rather than 0.09 ppm, for unclear reasons. In experiment (3), effects seen during the 60 minute exposure to 0.3 ppm (0.69 mg/m^3) were eye and throat irritation, increased eye blink frequency, and reduced respiratory rate.

In a study by Darley et al. (1960), 36 healthy human (student) volunteers were exposed (eyes only) to multiple substances (separately) and concentrations to determine eye irritancy. Only one substance and concentration combination was run on any given day. Subjects were exposed to acrolein at 0.06 ppm (0.14 mg/m^3), 1.3 – 1.6 ppm, or 2.0 – 2.3 ppm, for five minute periods. During exposure, the subjects wore activated carbon respirators so that they breathed clean air and only the eyes were exposed to the test mixture. Subjects were unaware of their exposures and could not observe other participants or the exposure equipment. Every 30 seconds, the participants rated the degree of eye irritation, with a scale of zero (no irritation), one (medium irritation), and two (severe irritation). The maximum value recorded by a subject during a test was used as the response of that subject to the exposure. The three exposure levels resulted in average eye irritation scores of 0.471, 1.182, and 1.476, respectively. These were relatively higher than the control group's ratings, which for three tests were reported as 0.361, 0.265, and 0.088. However, the rating values for eye irritation were not tested for statistical significance vs. controls. NAS/AEGL (2004) provide further discussion of the test methods.

A review by Kane and Alarie (1977) reported that acrolein levels of 0.5 to 2 ppm (1.15 to 4.6 mg/m^3) for 12 minutes or less caused lacrimation and varying degrees of eye irritation (ATSDR, 1990; EPA, 1986).

The American Conference of Governmental Industrial Hygienists (ACGIH) (1991, 1998) briefly discussed the key human studies that support recommended occupational exposure limits (OELs). While chronic data are lacking, short-term human exposure show that acrolein is intensely irritating to the eyes and upper respiratory tract, and higher levels of exposure can cause pulmonary edema and tracheobronchitis. According to their literature review, the human "irritation threshold" was reported to be 0.25 ppm (0.58 mg/m^3) to all mucous membranes within five minutes. They noted that sensitization can be produced from prolonged or repeated contact, but did not further describe this and did not cite a specific information source.

B. Summary of the Occupational Exposure Limits for Acute Exposure:

Review of the OELs (from ACGIH, NIOSH, and the OSHA) and their bases lends perspective to the acute human toxicity of airborne acrolein, although it should be emphasized that these limits are intended to protect a healthy adult worker population from significant health effects from discontinuous exposure over a work shift or portions of work shifts. Prior to 1998, the ACGIH (1991) had a threshold limit value (TLV) - time-weighted average (TWA) (for an eight-hour workday and a 40-hour work week) of 0.1 ppm (0.23 mg/m^3) and a TLV - short-term exposure limit (STEL) (15 minute exposure not to be exceeded at any time) of 0.3 ppm (0.69 mg/m^3). In 1998, ACGIH (1998) eliminated the TLV-TWA and TLV-STEL and set a TLV-Ceiling at 0.1 ppm (0.23 mg/m^3). A "TLV-Ceiling" is the concentration that should not be exceeded during any part of the working exposure. The rationale for the change in the recommendation was that acrolein is a rapidly-acting irritant and it is extremely potent compared to other aldehydes (ACGIH, 1998).

The NIOSH (1997) has recommended exposure limits (RELs) of a TWA of 0.1 ppm (0.23 mg/m^3) (for up to a ten-hour workday) and a STEL of 0.3 ppm (0.69 mg/m^3). The STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday. The NIOSH (1997) also recommends an IDLH level of 2 ppm (4.6 mg/m^3)

The OSHA established a workplace standard which is a permissible exposure limit, eight-hour workshift average, at 0.1 ppm (2.3 mg/m^3) (NIOSH, 1997).

C. Assessments of the Human Acute Toxicity Information by Various Agencies:

The following text and Table 1 summarize the development of acrolein acute environmental health benchmarks by CalEPA-OEHHA, ATSDR, and NAC/AEGL. Additionally, it may be noted that the EPA (IRIS) program agenda had included acrolein risk assessment for acute exposures (IRIS Tracking System, 2006; 97 FR No. 97, p. 29149, May 19, 2006). However, that effort has apparently been abandoned (Inside EPA's Risk Policy Report, 11/20/07; 4/3/07; 1/23/07).

1. CalEPA-OEHHA AREL

The CalEPA-OEHHA (1999) develops acute reference exposure levels (ARELs) for airborne toxicants, designed to protect all members of the general public, including

sensitive subgroups. The ARELs for protection from mild effects are designed for one-hour peak exposures which may occur only intermittently (e.g., once every two weeks).

In November 2007, CalEPA-OEHHA (2007a, 2007b) released public review drafts of the Technical Support Document (TSD) for the Derivation of Noncancer Reference Exposure Levels, and, Acrolein Reference Exposure Levels, respectively. The draft acrolein AREL is 1.0 ppb (2.3 ug/m^3), based on subjective ocular irritation (Darley et al., 1960). The AREL is derived from the 5-minute LOAEL of 0.06 ppm, UF_L=6, and UF_H= 10. The UF_H is based on a toxicokinetic subfactor of 1 (site of contact; no systemic effects) and a toxicodynamic factor of 10 (greater susceptibility of children to asthma exacerbation). They clarified that ocular irritation is not expected to be substantially different between children and adults. There is no evidence that infants and children have different or more irritancy receptors than adults (CalEPA-OEHHA, 2007a). Based on modeling of adults and 3-month old children that takes into account age-related ventilation rates and respiratory tract surface area, the deposition kinetics of reactive gases are generally thought not to be greatly different between adults and children (CalEPA-OEHHA, 2007b). However, acrolein has a potential to exacerbate asthma via a respiratory irritant effect, which can differentially affect infants and children. Therefore, the UF_H= 10 is assigned to account for potential asthma exacerbation (CalEPA-OEHHA, 2007b). The UF_L= 6 for the "mild effect" is consistent with their draft TSD; based on an analysis by Alexeeff et al. (1997) of LOAEL to NOAEL ratios for over 100 datasets, the 95th percentile of that ratio is 6.2. (More recently, Alexeeff et al. (2002) reported that for 215 datasets for 36 HAPs, mild acute inhalation LOAEL-to-NOAEL ratios were 2.0, 5.0, 6.3, and 10.0 for the 50th, 90th, 95th and 99th percentile, respectively.) Therefore, OEHHA applies a default value of 6 (targeting the 95th percentile of the relationship) to extrapolate from the LOAEL to the NOAEL when the effect is mild. Further, the TSD categorizes as mild adverse effects any symptoms of mild subjective complaints such as eye, nose, and throat irritation, with few to no objective findings. A time-adjustment factor to relate the 5" exposure duration to a 1-hr period was not applied, consistent with the TSD, which states that Haber's Law will not be normally applied for acute mild sensory irritancy. The rationale is that the level of response is likely dependent on only the concentration within the 1-hour time scale of concern for acute REL derivation, based on observations with other substances. Response to mild sensory irritants is mediated through binding to the trigemninal nerve receptors, the degree of which is determined by the exposure level and tissue concentration but not the duration of exposure once equilibrium is reached (which generally occurs relatively quickly). Therefore, irritancy is primarily a function of the air concentration, and not the total dose. Therefore, OEHHA considers trigeminally-mediated sensory irritant endpoints to be independent of the duration over the 1-hour timescale, unless data indicate such time dependence. They noted that this position is consistent with that of the NAC/AEGL, and that the NAS has suggested that Haber's Law does not apply for "some irritants" (CalEPA-OEHHA, 2007a). CalEPA-OEHHA (2007b) also stated that the ocular mucosa and nasal mucosa are both innervated by the cranial nerve V (trigeminal nerve), and that multiple studies with various substances indicate that ocular and nasal irritancy dose-response are similar in magnitude, indicating that the ocular irritancy dose-response for acrolein in Darley et al. (1960) is expected to also reflect irritancy of the upper respiratory tract.

CalEPA-OEHHA (2007b) also evaluated the results of Weber-Tschopp et al. (1977) and found that it supported the derivation of the AREL from the Darley et al. (1960) results. They referred to experiment (1) involving exposure to an increasing concentration of acrolein during a 40 minute period. They considered the LOAEL for significant ocular irritation to be first reported at 0.07 ppm, although it should be noted that the study authors and other reviewers (NAC/AEGL, 2004a) reported that the LOAEL for that experiment was 0.09 ppm. CalEPA-OEHHA (2007b) applied the same UFs and rationale to this LOAEL (0.07 ppm) as for the Darley et al. (1960) LOAEL (0.06 ppm), and derived a very similar AREL of 2.7 ug/m^3 (1.2 ppb).

Previously, CalEPA-OEHHA (1999) established an AREL of 0.09 ppb (0.19 ug/m^3). That was based on the LOAEL of 0.06 ppm (0.14 mg/m^3) (Darley et. al., 1960) for five minutes duration, which was extrapolated via time adjustment (5"/60") to an equivalent one-hour level of 5 ppb (11.5 ug/m^3). This was then divided by a UF_H of 10, and a UF_L of 6, to derive the AREL of 0.09 ppb (0.19 ug/m^3). This approach was also presented in a publication by OEHHA staff (Collins et al., 2004).

2. ATSDR acute MRL

The ATSDR (1990) established an acute (14 days or less) MRL of 0.115 ug/m^3 (0.05 ppb) in 1990. That was based on Weber-Tschopp et al. (1977) and an eye irritation LOAEL at 40 minutes exposure to 391 ug/m^3 (0.17 ppm), which was selected by a process that is unclear to this reviewer; experiment (1) reported an eye irritation LOAEL of 0.09 ppm with a 40 minute exposure. They applied a total UF=100 (UF_H= 10, UF_L= 10), and a time-adjustment of 40"/1440" per day, to derive this MRL. Since this time adjustment from 40 minutes to one-day was apparently used, it appears that the acute inhalation MRL was derived on the basis of a one-day exposure.

ATSDR (2005) released a draft revision to the acute MRL. The acute MRL was finalized (ATSDR, 2007) with the same derivation and value as in ATSDR (2005): 7 ug/m^3 (3 ppb). Based on experiment (3) of Weber-Tschopp et al. (1977), the acute MRL was derived from the LOAEL of 0.3 ppm (690 ug/m^3) for nose & throat irritation, and decreased respiratory rate, during the 1-hr exposure. They noted that the intensity of nose irritation reached a maximum mean score of 2 ("a little") at approximately 40 minutes into the exposure, with no change for the remaining exposure period. Intensity of throat irritation reached a maximum mean score of between 1 ("not at all") and 2 ("a little") at approximately 40 minutes into the exposure, with no increase in intensity scores for the remaining exposure period. Intensity of nose and throat irritation was scored significantly higher than pre-exposure values beginning at 10 minutes. A 20% decrease in respiratory rate was observed, compared to pre-exposure values. Further discussion of the selection of the chosen uncertainty factors, or the issue of time period adjustment, was not provided.

ATSDR (2005) also noted experiment (1) of Weber-Tschopp et al. (1977), involving gradually increasing exposure concentrations for 40 minutes. Subjects reported "a little" or "medium" irritancy at approximately 0.26 ppm (15 minutes into the exposure period), which was statistically different from controls, yet the changing concentrations made it difficult to fix the duration or level of exposure that was actually responsible for the onset

of significant irritation. The Darley et al. (1960) study was not cited by ATSDR (2007; 1990).

3. NAC AEGL

Under the authority of the Federal Advisory Committee Act, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL) was created. AEGLs are developed for accidental release emergency planning, and once-in-a-lifetime short-term inhalation exposures. The AEGL values are applicable to the general population, including infants and children and other individuals who may be sensitive or susceptible. AEGLs are set at exposure periods ranging from 10 minutes to 8 hours. Different AEGL levels are established, representing varying degrees of severity of toxic effects. At levels at or above the AEGL-1, levels could result in notable discomfort, irritation, or certain asymptomatic, nonsensory effects in the general population, although the effects would not be disabling and would be transient and reversible upon cessation of exposure. At levels at or above the AEGL-2 level, there could be irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. At levels at or above the AEGL-3 level, there could be life-threatening health effects or death (EPA, 2002).

The NAC/AEGL (2008) website indicates that the interim AEGL-1 values for 10", 30", 60", 4 hr and 8 hr are all set at 0.030 ppm (30 ppb, or 69 ug/m^3). These values have "interim" status, because they are based on peer review and consideration by the NAC/AEGL of public comment on Proposed AEGLs, and they await peer review by the National Research Council (NRC) and publication of Final AEGLs.

The AEGL development documents (NAC/AEGL, 1998, 2004a) discuss all of the best available, relevant data considered by NAC/AEGL. The AEGL-1 values were derived from the study by Weber-Tschopp et al., 1977. The critical effect is eye irritation and "annoyance"/discomfort, which occurred at a threshold of 0.09 ppm (0.207 mg/m^3). They applied an UF_H of 3 to derive the AEGL-1 from this threshold level, "…to account for sensitive individuals since irritant effects are not expected to vary greatly between individuals." (NAC/AEGL, 1998). They noted that the UF_H of 3 is considered sufficient due to the steepness of the concentration-response curve seen with acute rat exposures and lethality (NAC/AEGL, 2004a). With regard to the consistency of the AEGL-1 values over the time periods from 30 minutes to eight hours, the values were held constant across time since minor irritancy is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect (NAC/AEGL, 1998, 2004a). The UF_L= 1 is consistent with the level of protection intended for the AEGL-1, i.e., reversible irritation. Darley et al. (1960) was not cited.

MDEQ-AQD submitted comments on the NAS/AEGL (2004a) proposed AEGLs for acrolein (Sills, 2004). Specifically, it was requested that consideration be given to: the Darley et al. (1960) study findings; the UF_H of 3 versus 10; and, the lack of accounting for possible time-dependence in setting the same AEGL-1 value for various time periods. NAS/AEGL (2004b) provided responses to those comments. They provided a summary of the Darley et al. (1960) study, but stated that the Weber-Tschopp et al. (1977) study was more robust and utilized better methodology and analytical techniques than the Darley study, and was more appropriate as a key reference since it was an

inhalation exposure rather than just an ocular exposure. They noted that the Darly et al. (1960) study did not provide a clear concentration-response with regard to irritation at the 0.06 ppm level; the filtered air irritation score (0.361) and 0.06 ppm acrolein score (0.471) are both <0.5, where 0 is defined as “no irritation” and 1 is defined as “medium irritation”; therefore, both the air control and 0.06 ppm may have caused “slight irritation”. They indicated that they typically apply a $UF_H = 3$ for minor irritation, as with this case. They added that, “…minor ocular contact irritation is unlikely to vary greatly between humans”. They stated that AEGL-1 values are often held constant across time for sensory irritants, as described in their Standard Operating Procedures (SOP), because this endpoint is considered a threshold effect, and prolonged exposure will not result in an enhanced response. “In fact, individuals may adapt or become inured to sensory irritation provoked by exposure to these chemicals over these exposure periods such that the warning properties are reduced” (NAC/AEGL, 2004b). The Committee decided to raise the proposed acrolein AEGLs to “interim” status without modification.

Table 1: Acrolein Acute Inhalation Toxicity: Health Benchmarks for Public Health Protection and Derivation Basis.

Agency / Group	Health-based benchmark; ug/m3 (ppb)	Target population, level of protection intended	Key study, risk assessment point of departure	Benchmark derivation steps and factors
MDEQ-AQD ITSL (1-hr AT) (2000)	0.5 ug/m^3	Everyone, including susceptible subpopulations; no adverse effects.	a) Weber-Tschopp et al. (1977): LOAEL = 210 ug/m^3 (0.09 ppm) for 5" (experiment (1)) b) Darley et al. (1960): LOAEL=140 ug/m^3 (0.06 ppm) for 5"	Approximate average of **a)** 0.58 (from LOAEL=210 ug/m^3 UF_H=10, UF_L=3, time adjust=5"/60"), and, **b)** 0.39 ug/m^3 (from LOAEL=140 ug/m^3, UF_H=10, UF_L=3, time adjustment= 5"/60")
NAC/AEGL Committee of EPA (2004) interim AEGL-1 (for 10", 30", 1 hr, 4 hr, and 8 hr ATs)	69 ug/m^3 (30 ppb)	Everyone, including susceptible subpopulations; emergency, once-in-a lifetime esposure; mild effects may occur at this level.	Weber-Tschopp et al. (1977): eye irritation LOAEL=210 ug/m^3 (0.09 ppm) (experiment (1))	LOAEL= 210 ug/m^3, UF_H=3, no time period adjustment, and UF_L=1 as consistent with the intended level of protection
ATSDR (2007) acute MRL (for up to 14 days)	6.9 ug/m^3 (3 ppb)	Everyone, including susceptible subpopulations; no adverse effects.	Weber-Tschopp et al. (1977): nose & throat irritation, & decreased resp. rate, during the 1-hr exposure at 0.3 ppm (690 ug/m^3) (experiment (3))	LOAEL= 690 ug/m^3 (0.3 ppm), no time adjustment, total UF = 100 (UF_H=10, UF_L=10)
CalEPA-OEHHA (2007 draft) AREL (1 hr AT)	2.3 ug/m^3 (1.0 ppb)	Everyone, including susceptible subpopulations; no adverse effects; protective against peak 1 hr intermittent exposures.	Darley et al. (1960): mild eye irritation LOAEL = 140 ug/m^3 (0.06 ppm)	LOAEL= 140 ug/m^3, UF_H=10, UF_L=6, no time adjustment.
CalEPA-OEHHA (1999) and Collins et al. (2004) AREL (1 hr AT)	0.19 ug/m^3 (0.09 ppb)			LOAEL= 140 ug/m^3, UF_H=10, UF_L=6, time adjustment= 5"/60".

D. Derivation of an ITSL Protective of Acute Effects:

As shown in Table 1, various agencies have utilized in different ways the two key human acute exposure studies, to derive health-based benchmarks for various purposes. The most critical acute effect in humans has been shown to be irritancy, with a LOAEL demonstrated within 5 minutes in the two key studies. Although the Weber-Tschopp et al. (1977) study was more rigorously conducted and reported, the findings of the two studies are in agreement. The Darley et al. (1960) study is sufficient and appropriate for ITSL development; the lower LOAEL is provided by this study (albeit

only to a modest degree: LOAEL= 0.06 ppm at 5", vs. 0.09 ppm at 5" in experiment (1) of Weber-Tschopp et al. (1977).

It is not desirable to establish an ITSL with an AT of less than 1 hour, for practical purposes of compliance demonstrations (dispersion modeling, and potentially, establishing emission limits and emission testing requirements). Time adjustment is problematic, because the preferred way to adjust an acute dose-response to an equivalent longer-term dose-response is to have chemical-specific information, or a reasonable assurance that the adjustment has an appropriate basis. For some substances, the equivalency of (concentration X time) is an appropriate basis for relating the dose-responses for different exposure periods, while for other substances it is not. In the current ITSL, the critical effect of irritation in 5 minutes was time-adjusted to a 1 hr averaging time by a simple (default) approach of multiplying the concentration by (5"/60"), i.e., a factor of 12. However, as noted above, it has been argued by CalEPA-OEHHA (2007a, 2007b) and NAC/AEGL (2004a, 2004b) that in the particular case of the mild inhalation irritancy or acrolein, time adjustment up to a 1 hour time period is not appropriate. Time period adjustment is not recommended for the present ITSL derivation; the recommended acute ITSL based on the irritancy at 5" exposure is applied with a 1 hour AT without adjustment. This represents a change from the current acute ITSL derivation.

The recommended $UF_L = 10^{0.5}$, rather than 10, based on the relatively mild effect of irritancy demonstrated in Darley et al. (1960) as well as in the supporting study at 0.09 ppm (Weber-Tschopp et al., 1977). This does not represent a change from the current acute ITSL derivation.

The recommended $UF_H = 10$. ATSDR (2007) utilized $UF_H = 10$ for the acute MRL (without discussion). CalEPA-OEHHA (2007a, 2007b) provide arguments that there should be little difference in acute irritation sensitivity between adults and children. Nevertheless, the key studies entailed healthy young adults, and indicated that there was some interindividual variability in response. Therefore the default $UF_H = 10$ appears appropriate to account for potentially greater sensitivity of some individuals in the general population. This issue may be reconsidered with future reassessments. CalEPA-OEHHA (2007a) justified $UF_H = 10$ based on a concern for potential asthma exacerbation, however, there are no studies supporting that an additional UF= 10 is appropriate or necessary to protect against that possibility; the recommended $UF_H = 10$ and total UF=30 may be considered adequate to address that concern.

Therefore, the recommended acrolein acute (1 hour) ITSL is derived as follows:

$$\frac{\mathbf{140\ ug/m^3}}{\mathbf{10^{0.5}\ X\ 10}} \sim \frac{\mathbf{140\ ug/m^3}}{\mathbf{3\ X\ 10}} = \mathbf{4.67\ ug/m^3} \sim \mathbf{5\ ug/m^3\ (1\ hour\ AT)}$$

Where,
LOAEL = 140 ug/m^3 (Darley et al. (1960)
$UF_L = 10^{0.5}$
$UF_H = 10$

II. Chronic noncancer risk assessment:

The EPA (2003a) has developed a Reference Concentration (RfC) of 0.02 ug/m^3 for the protection of all individuals with a lifetime exposure to acrolein. The AQD has adopted this value for an ITSL with an annual averaging time, coupled with the 1 hr ITSL to ensure protection from the short-term irritancy of acrolein.

Acrolein has a high vapor pressure and is highly water soluble, and is very biologically reactive to aqueous membranes. There is ample evidence that the irritant effect (in the upper respiratory tract and eyes) is the critical effect for risk assessment of chronic exposures. There is a lack of developmental effects studies, and some limited reproduction/fetal development studies which are negative. The best animal studies are subchronic in duration. There is a lack of chronic animal or human inhalation studies, and oral studies are not considered to be pertinent to the portal-of-entry effects of acrolein in the respiratory tract.

The RfC of 0.02 ug/m3 was originally verified by EPA in 1991. In 2003, EPA updated the interpretation of the database, but the RfC remained unchanged. The updated literature search by AQD failed to discover any additional key studies for long-term risk assessment. The RfC is based on a subchronic (3 month) rat inhalation study, finding a LOAEL for nasal lesions at an exposure level of 900 ug/m3 (Feron et al., 1978). The LOAEL (adjusted) = 160 ug/m3. Dosimetric adjustment utilized an RGDR (regional gas dose ratio used in derivation of a human equivalent concentration [HEC] for gases) of 0.14. The LOAEL (HEC) = 20 ug/m3. A total UF = 1000 was applied, consisting of:
$UF_A = 3$
$UF_H = 10$
$UF_S = 10$
$UF_L = 3$
$UF_D = 1$

The EPA's confidence in the RfC was rated as "medium" for the key study, "low to medium" for the database, and "medium" for the RfC.

ATSDR (2007) did not derive a chronic inhalation MRL, due to an inadequate database.

CalEPA-OEHHA (2007b) has drafted an acrolein chronic REL = 0.12 ug/m3 (0.05 ppb), based on two rat inhalation studies reporting lesions in the respiratory epithelium in rats exposed for 62 days (Kutzman et al., 1985) or 13 weeks (Feron et al, 1978). For each study, they derived the chronic REL as follows: LOAEL= 0.4 ppm, $LOAEL_{HEC}$= 60 ppb (with time adjustment and DAF=0.85), total UF= 1200. The total UF= 1200 is composed of UF_L= 6 (mild effect); UF_S= $10^{0.5}$ (because exposure was 8-12% of lifetime); UF_{A-k}= 2 (besides the dosimetric adjustment); UF_{A-d}= $10^{0.5}$ (default); UF_{H-d}= 10 (concern for potential asthma exacerbation in children). They compared their chronic REL (0.12 ug/m3) derivation to the EPA (2003) IRIS RfC of 0.02 ug/m3, which was based on the same LOAEL from Feron et al. (1978). Besides the different UFs applied, CalEPA-OEHHA (2007b) considered preferable their DAF of 0.85 (versus EPA's use of an RGDR of 0.14). Their position is that the DAF of 0.85 better accounts for differences in

rat and human exposures to reactive gases, based on comparative modeling of gas flux in human and rat nasal passages (CalEPA-OEHHA, 2007b). This issue may be reconsidered by AQD in future reassessments.

Chronic ITSL

The above data review does not indicate that the EPA RfC value and chronic ITSL are inappropriate. The data review supports the continued use of an annual averaging time with the chronic ITSL of 0.02 ug/m^3 to ensure protection from adverse effects with long-term exposures.

References

ACGIH. 1991. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th Edition.

ACGIH. 1998. 1998 Supplements to ACGIH (1991).

Alexeeff, G.V. et al. 2002. Characterization of the LOAEL-to-NOAEL uncertainty factor for mild adverse effects from acute inhalation exposures. Regulatory Toxicology and Pharmacology 36(1): 96-105.

Alexeeff, G.V. et al. 1997. Stochastic evaluation of acute inhalation thresholds from reported LOAELs [Abstract #851]. The Toxicologist 36 (1 Part 2): 167.

ATSDR. 2007. Toxicological Profile for Acrolein. U.S. DHHS. Finalized August 2007 (available online only).

ATSDR. 1990. Toxicological Profile for Acrolein. U.S. DHHS. TP-90-01.

California EPA Office of Environmental Health Hazard Assessment (CalEPA-OEHHA). 2007a. Acrolein Reference Exposure Levels. Public Review Draft: Nov. 2, 2007.

California EPA Office of Environmental Health Hazard Assessment (CalEPA-OEHHA). 2007b. Air Toxics Hot Spots Risk Assessment Guidelines. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Public Review Draft: November 2007.

California EPA Office of Environmental Health Hazard Assessment (CalEPA-OEHHA). 1999. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part 1. The Determination of Acute Reference Exposure Levels for Airborne Toxicants.

Collins, J.F., et al. 2004. Development of acute inhalation reference exposure levels (RELs) to protect the public from predictable excursions of airborne toxicants. J Appl Toxicol. 24(2): 155-66.

Darley, E.F., et al. 1960. Plant damage and eye irritation from ozone-hydrocarbon reactions. Agricultural and Food Chemistry 8(6): 483-485.

EPA. 2003a. Integrated Risk Information System (IRIS database). Chemical file for acrolein. RfC and RfD last revision date 6/3/03.

EPA. 2003b. Toxicological Review of Acrolein. In support of summary information on the Integrated Risk Information System (IRIS). May 2003. EPA/635/R-03/003.

EPA. 1991. Integrated Risk Information System (IRIS database). Chemical file for acrolein. RfC Verification date 4/25/91.

EPA. 1986. Health Assessment Document for Acrolein. OHEA. EPA-600/8-86-014A. Review Draft.

Feron, V.J. et al. 1978. Repeated exposure to acrolein vapor: Subacute studies in hamsters, rats and rabbits. Toxicology 9: 47-57.

Kane, L.E., and Y. Alarie. 1977. Sensory irritation to formaldehyde and acrolein during single and repeated exposures in mice. Amer. Ind. Hyg. Assoc. 38: 509-522.

Kutzman, R.S., et al. 1985. Changes in rat lung structure and composition as a result of subchronic exposure to acrolein. Toxicology 34:139-151.

National Advisory Committee/AEGL (NAS/AEGL). 2007. Acrolein interim AEGLs. http://www.epa.gov/oppt/aegl/pubs/results82.htm Retrieved 1/8/08.

National Advisory Committee/AEGL (NAS/AEGL). 2004a. Proposed Acute Exposure Guideline Levels (AEGLs). Acrolein. Proposed 1/2004.

National Advisory Committee/AEGL (NAS/AEGL). 2004b. Final Meeting-35 Highlights. National Advisory Committee (NAC) for Acute Exposure Guideline Levels (AEGLs) for Hazardous substances. December 13-15, 2004. (Includes responses to Federal Register comments on the proposed AEGL values).

National Advisory Committee/AEGL (NAS/AEGL). 1998. Draft. Acute Exposure Guideline Levels (AEGLs) for Acrolein. February 1998 Draft.

NIOSH. 1997. NIOSH Pocket Guide to Chemical Hazards. U.S.DHHS.

Sills, R. 2004. Memo from Robert Sills, MDEQ-AQD to EPA docket ID Number OPPT-2004-0079. October 7, 2004.

Weber-Tschopp, A., et al. 1977. Experimentally induced irritating effects of acrolein on men. Int. Arch. Occup. Environ. Hlth. 40:117-130.