Development Support Document
24-Hour AMCV
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Acrolein

CAS Registry Number: 107-02-8

24-Hour Ambient

Air Monitoring Comparison Value

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ACRONYMS AND ABBREVIATIONS

Acronyms and Abbreviations	Definitions
AMCV	Air Monitoring Comparison Value
°C	degrees Celsius
CNS	central nervous system
d	day
DSD	development support document
ET	extrathoracic
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not 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 nonthreshold dose response cancer effect
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
h	hour(s)
H	humans
HEC	human equivalent concentration
HQ	hazard quotient
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
µg	microgram

Acronyms and Abbreviations	Definitions
$\mu g/m^3$	micrograms per cubic meter
mg	milligrams
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
n	number
N/A	Not applicable
NOAEL	no-observed-adverse-effect-level
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
ReV	reference value
RGDR	regional gas dose ratio
SD	Sprague-Dawley
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
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
USEPA	United States Environmental Protection Agency
w	week

Chapter 1 Summary Tables

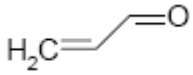
Table 1 provides the health-based 24-hour (h) Reference Value (ReV) from an acute evaluation of acrolein, which is used as the 24-h Air Monitoring Comparison Value (AMCV) for evaluation of 24-h ambient air monitoring data. The 24-h AMCV was developed based on the Guidelines for Developing 24-Hour Reference Values (TCEQ 2014a) and the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). Please refer to the Acrolein Development Support Document (DSD) (TCEQ 2014b) for details on how other acute and chronic values in Table 1 were derived and are used for review of ambient air monitoring data. Table 2 provides chemical/physical properties.

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

Short-Term Values	**Concentration**	**Notes**
1-h AMCV	11 µg/m^3 (4.8 ppb) [a] **Short-Term Health**	**Critical Effect(s):** eye, nose, and throat irritation and decreased respiratory rate in human volunteers
24-h AMCV	11 µg/m^3 (4.8 ppb) **24-h AMCV**	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) [a] **Odor**	50% odor detection threshold; piercing, disagreeable odor
$^{acute}ESL_{veg}$	230 µg/m^3 (100 ppb) [a] **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) [a] **Long-Term Health**	**Critical Effect(s):** Mild hyperplasia and lack of recovery of the respiratory epithelium in Fisher 344 rats
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	- - -	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	- - - [a] **Long-Term Vegetation**	No data found

[a] TCEQ (2014b)

Table 2 Chemical and Physical Data

Parameter	**Value**	**Reference [a]**
Molecular Formula	C_3H_4O	ATSDR 2007
Molecular Weight	56.1	TCEQ 2014b
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 2014b
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 2014b
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 1 mg/m^3 = 0.44 ppm	Toxicology Staff

[a] Refer to TCEQ (2014b) for references

Chapter 2 Background

For chemicals detected in the ambient air monitoring network, short-term AMCVs have generally been derived by the TCEQ to evaluate 1-h reported concentrations and long-term AMCVs were derived to evaluate annual averages. Since a significant amount of ambient air data is collected over a 24-h duration, the derivation of chemical-specific 24-h AMCV values is needed to better evaluate ambient 24-h data. TCEQ believes using a short-term, 1-h AMCV or long-term AMCV to evaluate a 24-h ambient air sample is not appropriate because toxic effects induced by 24-h exposure may be governed by modes of action that are somewhat different than those influencing toxicity due to a 1-h or chronic exposure. A 24-h Reference Value (ReV) is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a 24-h exposure. The ReV is used as the AMCV (TCEQ 2012).

The critical step in deciding whether or not to derive a 24-h AMCV is the availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-h exposure duration. An evaluation of the mode of action, dose metric, and the toxicokinetics and toxicodynamics of the chemical of concern, as well as exposure duration adjustments that are unique for the derivation of a 24-h AMCV, is conducted. The same analytical steps used to derive acute 1-h AMCVs and chronic AMCVs (TCEQ 2012) are used to derive a 24-h AMCV. OECD (2010) also provides guidance applicable to the development of acute reference concentrations.

The purpose of this document is to summarize the main steps involved in the development of the 24-h AMCV for acrolein. General steps for developing a 24-h value, discussed in detail below, include:

- availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-h exposure duration;
- identification of a point of departure (POD) for the critical effect(s) based on review of dose-response data for relevant toxicity endpoints;
- consideration of an exposure duration adjustment;
- animal-to-human inhalation dosimetric adjustment;
- selection and application of applicable uncertainty factors; and
- derivation of the 24-h AMCV.

Please refer to the Acrolein DSD (TCEQ 2014b) for detailed information on physical/chemical properties and mode of action information.

Chapter 3 Acute 24-H AMCV

3.1 Key Studies and Potential Points of Departure

Acrolein's toxicity is primarily concentration dependent and levels causing adverse effects are very similar in humans and animals. Exposure to acrolein vapors can cause respiratory irritation, eye and nose irritation, and at higher levels, severe respiratory tract irritation and lacrimation (ATSDR 2007). Four studies were considered for the development of a 24-h AMCV (Roemer et al. 1993, Cassee et al. 1996, Weber-Tschopp et al. 1977, and Dorman et al. 2008). The two studies with sufficient quality were identified as key studies and carried through the 24-h AMCV derivation process: Weber-Tschopp et al. (1977) and Dorman et al. (2008).

- In Weber-Tschopp et al. (1977), male and female healthy college students (21 males and 25 females) were exposed to various concentrations of acrolein. Various exposure durations and exposure concentrations were evaluated by the authors; however, the longest exposure duration was 60 min. A minimal lowest observed adverse effect level (LOAEL) of 0.3 ppm acrolein after 60 min of exposure was identified based on mild eye, nose, and throat irritation and decreased respiratory rate. This key study LOAEL was used for the derivation of a candidate 24-h AMCV.

- Dorman et al. (2008) anotherexposed adult male F344 rats (12 rats/exposure concentration/time point) to acrolein at concentrations of 0, 0.02, 0.06, 0.2, 0.6, or 1.8 ppm, 6 h/d, 5 d/wk for 4 d up to 65 d. Respiratory tract histopathology was evaluated after all exposure durations. The exposure duration chosen as most appropriate for development of the 24-h AMCV was a 4-d exposure duration (6 h/day for 4 d = 24 hours of exposure). A no observed adverse effect level (NOAEL) of 0.2 ppm and a LOAEL of 0.6 ppm were identified for this study based on the incidence of nasal respiratory epithelial hyperplasia and epithelial squamous metaplasia. The NOAEL from this key study was used for the derivation of a candidate 24-h AMCV.

3.2 Critical Effects

Eye, nose, and respiratory tract irritation is the most sensitive endpoint for short-term exposure to acrolein. The TCEQ developed a 1-h AMCV of 4.8 ppb (TCEQ 2014b) based on eye, nose, and throat irritation and decreased respiratory rate in human volunteers following a 1 h exposure to 0.3 ppm acrolein (Weber-Tschopp et al. 1977).

The Dorman et al. (2008) key study examined a number of endpoints and identified a NOAEL and LOAEL, with the LOAEL for nasal respiratory epithelial hyperplasia and epithelial squamous metaplasia being higher than that for the irritation (the most sensitive endpoint)

observed in the Weber-Tschopp et al. (1977) study. Since the irritative effects of acrolein are mainly concentration-dependent, concentrations producing adverse effects are similar in humans and animals, regardless of exposure duration.

3.3 Toxicokinetics and Mode of Action

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 on exposures to acrolein (Beauchamp et al. 1985). These adverse, noncarcinogenic point-of-entry effects are presumed to have a threshold MOA (TCEQ 2012).

3.4 Dose Metric

In the two key 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.

3.5 Relevant Points of Departure (POD)

In the key study by Dorman et al. (2008), a NOAEL of 0.2 ppm acrolein was identified at which there was both an absence of nasal epithelial hyperplasia and epithelial squamous metaplasia. For this study, the relevant NOAEL-based POD is 0.2 ppm.

In the other 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 60 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 LOAEL-based POD is 0.3 ppm.

3.6 Duration and Default Animal-to-Human Dosimetry Adjustment

No duration adjustments were necessary for either key study (Dorman et al. 2008, Weber-Tschopp et al. 1977), as adverse effects following acrolein exposure are primarily concentration dependent.

Default animal-to-human dosimetry adjustments for the Dorman et al. (2008) study were based on methods for Category 1 gases producing portal of entry effects. The POD of 0.2 ppm was multiplied by the default dosimetric adjustment factor (DAF) of 1 because the critical effect is in the extrathoracic (ET) respiratory tract region (USEPA 2012). The human equivalent NOAEL-based POD (POD_{HEC}) is 0.2 ppm for the Dorman et al. (2008) study.

In the Weber-Tschopp et al. (1977) human study, the appropriate human equivalent concentration POD (POD_{HEC}) is the LOAEL of 0.3 ppm.

3.7 Uncertainty Factors

The default procedure for deriving health-protective concentrations for noncarcinogenic effects is to determine a PODHEC and apply appropriate uncertainty factors (UFs) (i.e., assume a threshold/nonlinear MOA) (TCEQ 2012).

3.7.1 Dorman et al. (2008) Study

The POD_{HEC} of 0.2 ppm (based on a NOAEL) was divided by the following UFs to derive a candidate 24-h ReV/AMCV:

- Intraspecies human UF (UF_H) of 10 for intraspecies variability (i.e., potentially sensitive human subpopulations);
- Interspecies animal UF (UF_A) of 3 for extrapolation from animals to humans to account for potential toxicodynamic species differences since a toxicokinetic dosimetric adjustment was already applied (DAF of 1); and
- Database UF (UF_D) of 1 for database uncertainty because the overall database of acute toxicological studies with acrolein is extensive (ATSDR 2007, NRC 2009), consisting of both human and animal studies as well as short-term reproductive/developmental studies.

Thus, the candidate 24-h ReV/AMCV =

POD_{HEC} / (UF_H x UF_A x UF_D) = 0.2 ppm/ (10 x 3 x 1)

= 0.0066 ppm

= 7 ppb (rounded to two significant figures)

3.7.2 Weber-Tschopp et al. (1977) Study

The POD_{HEC} of 0.3 ppm (based on a LOAEL) was divided by the following UFs to derive another candidate 24-h ReV/AMCV:

- Intraspecies human UF (UF_H) of 10 for intraspecies variability (i.e., potentially sensitive human subpopulations such as those with pre-existing respiratory conditions or diseases which may make them more sensitive to the irritant properties of acrolein.);
- LOAEL to NOAEL UF (UF_L) of 6.3 for the extrapolation of a LOAEL to NOAEL as the inhalation health effect was considered to be mild (TCEQ 2014). 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

- Database UF (UF_D) of 1 for database uncertainty because the overall database of acute toxicological studies with acrolein is extensive (ATSDR 2007, NRC 2009), consistingof both human and animal studies as well as short-term reproductive/developmental studies.

Thus, the candidate 24-h ReV/AMCV =

POD_{HEC} / (UF_H x UF_A x UF_D) = 0.3 ppm / (10 x 6.3 x 1)

= 0.0048 ppm

= 4.8 ppb

3.8 Choice of Critical Effect

The TCEQ identifies the relevant, adverse health effect observed at the lowest POD_{HEC} in an appropriate sensitive species as the critical adverse effect (TCEQ 2012). Thus, POD_{HEC} values corresponding to effect levels (e.g., LOAELs) are needed to make direct comparisons in order to identify the critical effect, since comparing NOAEL-type PODs or comparing PODs that are incomparable in regard to the occurrence of effects (e.g., NOAEL-based versus LOAEL-based POD_{HEC} values) cannot generally be relied upon to be informative regarding the first effect which may be expected to occur as concentrations rise (i.e., the critical effect).

The LOAEL-based POD_{HEC} of 0.3 ppm from the Weber-Tschopp et al. (1977) study was used to derive the final 24-h AMCV, as it was derived from a human study and is the lowest LOAEL-based POD_{HEC} from the two key studies (the LOAEL-based POD_{HEC} from Dorman et al. (2008) is 0.6 ppm) and therefore identifies the critical effect(s). Even though the exposure duration is 1-h, studies using exposure durations of less than 6 h are appropriate to use as the basis for a 24-h AMCV when available data indicate that the primary toxic effect induced by a chemical is primarily concentration-dependent, such as irritation (TCEQ 2014a).

The TCEQ Guidelines to Develop 24-Hour Inhalation Reference Values (TCEQ 2014a) states that if the value for the 24-h AMCV is less than or equal to the 1-h AMCV and greater than the chronic AMCV, it may be a reasonable and predictive value.

Table 3 shows the 24-h AMCV using the Weber-Tschopp et al. (1977) study.

Table 3 Derivation of the Acute 24-h AMCV (Weber-Tschopp et al. 1977)

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 24 h	NA
POD_{ADJ} (applicable to 24 h)	0.3 ppm
POD_{HEC}	0.3 ppm
Total Uncertainty Factors (UFs)	63
Interspecies UF	*NA*
Intraspecies UF	*10*
LOAEL UF	*6.3*
Incomplete Database UF *Database Quality*	*1* *High*
Acute 24 h AMCV	**11 µg/m^3 (4.8 ppb)**

3.9 Values for Air Monitoring Evaluation

The acute evaluation in TCEQ (2014) and this document resulted in the derivation of the following values:

- 24-h acute health-based AMCV = 11 µg/m^3 (4.8 ppb) (Weber-Tschopp et al. 1977)
- 1-h acute health-based AMCV = 11 µg/m^3 (4.8 ppb) (TCEQ 2014b)
- odor-based AMCV = 8.2 µg/m^3 (3.6 ppb) (TCEQ 2014b)
- short-term vegetation-based AMCV = 230 µg/m^3 (100 ppb) (TCEQ 2014b)

The health-based 24-h AMCV of 11 µg/m^3 **(**4.8 ppb**)** equals the TCEQ acute 1-h AMCV. It is sufficiently conservative for the adequate protection of public health for the exposure duration and adverse effects considered and would significantly complement TCEQ health effect evaluations of ambient air data, which currently only utilize 1-h and chronic (i.e., lifetime) health-protective and welfare-based (i.e., odor, vegetation) AMCVs.

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