Development Support Document
24-Hour AMCV
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Formaldehyde

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24-Hour Ambient
Air Monitoring Comparison Value

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ACRONYMS AND ABBREVIATIONS

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ADH	aldehyde dehydrogenase
AEGL	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
^{0} C	degrees centigrade
BMR	benchmark response
CNS	central nervous system
ConA	Concanavalin A
CRO	crotonaldehyde
DSD	development support document
EC_{50}	Effective concentration at a 50% response level
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
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level

Acronyms and Abbreviations	Definition
EU	European Union
GC	gas chromatography
GLP	good laboratory practice
hr	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
HEC	human equivalent concentration
HQ	hazard quotient
HSDB	Hazardous Substance Data Base
IARC	International Agency for Research on Cancer
IC_{50}	Inhibitory concentration at a 50% response level
IL	interleukin
IPCS	International Programme on Chemical Society
IRIS	USEPA Integrated Risk Information System
kg	kilogram
LC_{50}	concentration causing lethality in 50% of test animals
LD_{50}	dose causing lethality in 50% of test animals
LPS	lipopolysaccharide
LOAEL	lowest-observed-adverse-effect-level
LTD	Limited toxicity data
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter of air
mg	milligrams
mg/m^3	milligrams per cubic meter of air
min	minute

Acronyms and Abbreviations	Definition
MOA	mode of action
n	number
NAC	National Advisory Committee
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRC	National Research Council
OAEL	Observed adverse effect level
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
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
RD_{50}	50% reduction in respiration rate
ReV	reference value
RGDR	regional gas dose ratio
ROS	Reactive oxygen species
RP	Relative potency
RP_{GM}	Geometric mean of relative potency endpoints
SA	surface area
SD	Sprague-Dawley
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor

Acronyms and Abbreviations	Definition
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
V_E	minute volume

Chapter 1 Summary Table

Table 1 provides the health-based 24-hour (h) Reference Value (ReV) from an acute evaluation of formaldehyde, 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 Guidelines for Developing 24-Hour Reference Values (TCEQ 2014) and TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012). Please refer to the Formaldehyde Development Support Document (DSD) (TCEQ 2008) for details on how other acute and chronic values in Table 1 used for review of ambient air monitoring data were derived. Table 2 provides chemical/physical properties.

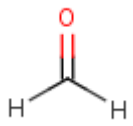
Table 1 Air Monitoring Comparison Values (AMCVs) for Ambient Air

Short-Term Values	**Concentration**	**Notes**
acute ReV [1 h]	**50 µg/m^3 (41 ppb) [a]** **1-h Short-Term Health**	**Critical Effect(s):** eye and nose irritation in human volunteers
acute ReV [24 h]	**30 µg/m^3 (24 ppb)** **24-h Short-Term Health**	**Critical Effect(s):** elevated rates of symptoms such as eye, nasal, and lower airway discomfort in workers
$^{acute}ESL_{odor}$	**620 µg/m^3 (500 ppb) [a]** **Odor**	50% odor detection threshold; pungent, highly irritating odor
$^{acute}ESL_{veg}$	---	concentrations producing vegetative effects were significantly above other ESLs
Long-Term Values	**Concentration**	**Notes**
chronic ReV (noncarcinogenic/threshold)	**11 µg/m^3 (8.9 ppb) [a]** **Long-Term Health**	**Critical Effect:** elevated rates of symptoms such as eye, nasal, and lower airway discomfort in workers
chronic ReV (carcinogenic/threshold)	**18 µg/m^3 (15 ppb) [a]** **Long-Term Health**	**Critical Effect:** cell proliferation/cytotoxicity in rats
$^{chronic}ESL_{veg}$	---	concentrations producing vegetative effects were significantly above other ESLs

[a] TCEQ (2008)

Abbreviations used in Table 1: **ppb**, part per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Level; **ReV**, Reference Value; **AMCV**, air monitoring comparison value; ^{acute}**ESL$_{odor}$**, acute odor-based ESL; ^{acute}**ESL$_{veg}$**, acute vegetation-based ESL; ^{chronic}**ESL$_{nonthreshold(c)}$**, chronic health-based ESL for linear dose-response cancer effect; and ^{chronic}**ESL$_{veg}$**, chronic vegetation-based ESL

Table 2 Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	CH_2O	ATSDR (1999)
Chemical Structure		ChemIDplus (2014)
Molecular Weight	33.03 (g/mole)	TRRP (2006)
Physical State	gas	ATSDR (1999)
Color	colorless	ATSDR (1999)
Odor	pungent, suffocating, highly irritating odor	ATSDR (1999)
CAS Registry Number	50-00-0	TRRP (2006)
Synonyms and Trade Names	Synonyms: formic aldehyde, methanal, methyl aldehyde, methylene oxide Trade Names: aqueous - Formalin, Formol, Morbicid, Veracur; polymeric form - Paraformaldehyde, Polyoxymethylene, Paraform, Formagene	ATSDR (1999)
Solubility in water	550,000 mg/L	TRRP (2006)
Low K_{ow}	0.35	TRRP (2006)
Vapor Pressure	3,880 mm Hg at 25°C	TRRP (2006)
Vapor Density (air = 1)	1.08	ACGIH (2001)
Density (water = 1)	0.815 g/ml at -20° C	ATSDR (1999)
Melting Point	-92° C	ATSDR (1999)
Boiling Point	-21° C	ATSDR (1999)
Conversion Factors	1 µg/m^3 = 0.813 ppb @ 25°C 1 ppb = 1.23 µg/m^3	ATSDR (1999)

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 have been 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. This consideration applies to formaldehyde since it is detected in the TCEQ ambient air monitoring network using 24-h DNPH cartridge samples. Without a 24-h AMCV for formaldehyde, only a very limited evaluation of the reported 24-h levels is possible because 1-h and chronic (i.e., lifetime) AMCVs are largely inappropriate for this purpose. Thus, the development of a 24-h AMCV is necessary for the best possible health effects evaluation of individual 24-h sample results, and would significantly complement the short-term and chronic evaluations of formaldehyde ambient air data.

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 (TCEQ 2014). 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 formaldehyde. General steps discussed below for developing a 24-h value include:

- identification of a point of departure 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 (if applicable);
- selection and application of applicable uncertainty factors; and
- derivation of the 24-h AMCV.

Please refer to the Formaldehyde Development Support Document (TCEQ 2008) for detailed information on human and animal studies, mode of action information, etc.

Chapter 3 Acute 24-h AMCV

In both human and animal noncarcinogenic studies, data suggest the most sensitive endpoint for long-term exposure to formaldehyde is irritation and associated respiratory symptoms. Since relevant human studies are available and preferable over animal studies, human studies were reviewed and used to develop the 24-h AMCV. The key study choosen for development of the acute 24-h AMCV was Wilhelmsson and Holmstrom (1992), the same key study used to develop the chronic ReV (TCEQ 2008). The TCEQ conservatively used the same point of departure (POD) that its chronic noncarcinogenic AMCV is based on because the exposure duration (8 h/day, 5 d/week) is more similar to the 24-h duration of interest than the 2-4 h exposure durations for the acute studies considered in deriving the 1-h ReV (TCEQ 2008). The following summary of Wilhelmsson and Holmstrom (1992) was taken from TCEQ (2008).

3.1 Key Study

Wilhelmsson and Holmstrom (1992) evaluated reported symptoms (e.g., nasal, lung, eye, skin, mucosal hyper-reactivity) in 66 workers chronically exposed (average of 10 years) to a mean formaldehyde concentration of 0.26 mg/m^3 (0.21 ppm). The mean formaldehyde concentration for the 36 members of the reference (control) group was 0.09 mg/m^3 (0.07 ppm). Formaldehyde concentrations were measured with personal sampling equipment (sampling tubes) in the ambient air of all worker worksites. The stated purpose of the study was to determine the mechanisms underlying symptoms (e.g., nasal) in exposed workers (i.e., direct irritation, hyper-reactivity in atopics, hyper-reactivity in nonatopics, immunologically-mediated type 1 (immediate) reaction to formaldehyde). *The study found that the rates of symptoms such as eye, nasal, and lower airway discomfort (e.g., cough, wheezing) were elevated in the formaldehyde-exposed workers as compared to the reference (control) group.*

The formaldehyde-exposed group was reported to contain a smaller percentage (11%) of atopics (as determined by a laboratory test) than the reference (control) group (33%). This difference suggests that atopics, who have Type 1 hypersensitivity or allergic reaction for which there is a genetic predisposition (Davis 1989), may have left the formaldehyde group. In the formaldehyde epicutaneous (skin) test, the formaldehyde-exposed group contained a greater percentage of workers with positive immediate or delayed skin reaction (30%) than the reference (control) group (17%). Blood serum levels of IgE antibodies to formaldehyde were also determined to assess the possible mechanism of IgE-mediated sensitization to formaldehyde, which would result in a type 1 (immediate) local inflammatory response (e.g., allergic rhinitis) upon exposure. Formaldehyde-exposed atopic subjects did not have a significantly higher rate of clinical symptoms related to the upper and lower airways, eyes, or skin. This finding is not in concordance with the general belief that atopic individuals are more prone to develop clinical symptoms in occupational environments. Of the formaldehyde-exposed workers with a positive skin test, 92% had clinical symptoms of the nose or lower airways. However, the study does not indicate whether this is significantly different from exposed workers without a positive skin test, and examination of data for the group as a whole does not suggest this since high percentages of formaldehyde-exposed workers experienced general and workplace-related nasal or lower airway symptoms. Additionally, there were no significant findings regarding IgE values in relation to symptoms. Therefore, while the study included potentially sensitive subgroups such as atopics and those with a positive skin reaction, these subpopulations did not demonstrate greater

sensitivity to formaldehyde or related symptoms (e.g., clinical symptoms related to the upper and lower airways, eyes, or skin). The LOAEL and NOAEL from this study based on eye, nasal, and lower airway discomfort are 0.26 mg/m^3 (0.21 ppm) and 0.09 mg/m^3 (0.07 ppm), respectively.

3.2 MOA and Dose Metric

The MOA by which formaldehyde may produce noncarcinogenic effects (e.g., eye/respiratory irritation) is discussed in TCEQ (2008). For the key and supporting studies, data on formaldehyde air concentrations for residents and occupationally-exposed workers are available. Formaldehyde air concentration is an appropriate dose metric for the chronic noncarcinogenic evaluation as air concentration is the dominant determinant of irritation in long-term studies.

3.3 Critical Effect and Point of Departure

The stated purpose of the key study was to determine the mechanisms underlying symptoms (e.g., nasal) in exposed workers (i.e., direct irritation, hyper-reactivity in atopics, hyper-reactivity in nonatopics, immunologically-mediated type 1 (immediate) reaction to formaldehyde). The rates of symptoms such as eye, nasal, and lower airway discomfort (e.g., cough, wheezing) were found to be elevated in the formaldehyde-exposed workers as compared to the reference (control) group. The POD_{HEC} was the NOAEL of 0.09 mg/m^3.

3.4 Duration Adjustments

An 8-to-24-h exposure duration adjustment was judged not to be necessary because the TCEQ conservatively used the same POD that its chronic noncarcinogenic AMCV is based on with exposure 8 h/d, 5 d/wk for 10 yrs **(**Wilhelmsson and Holmstrom 1992). Due to the similarity between acute and chronic effects levels, irritation appears to be primarily concentration dependent. Not performing this duration adjustment is consistent with other agencies (e.g., ATSDR 1999, CalEPA 2008).

3.5 Uncertainty Factors

The default procedure for deriving health-protective concentrations for noncarcinogenic effects is to determine a POD and apply appropriate uncertainty factors (UFs) (i.e., assume a threshold/nonlinear MOA) (TCEQ 2012). The POD_{HEC} of 0.09 mg/m^3 was used and divided by the following UFs:

- Intraspecies human UF (UF_H) of 3 for intraspecies variability; and
- Database UF (UF_D) of 1 when evaluating database uncertainty.

A UF_H of 3 was selected since although the study included potentially sensitive subgroups (i.e., atopics, those with a positive skin reaction), there is a potential for a healthy worker effect (i.e., sensitive workers could have left the formaldehyde-exposed group), and the scientific literature indicates a broad range of reported human susceptibility to the irritating properties of airborne formaldehyde (ACGIH 2001).

A UF_D of 1 was selected because the overall toxicological database for formaldehyde is extensive as there are numerous studies available that evaluate a variety of respiratory, systemic, neurological and immunological endpoints.

$$24\text{-h ReV} = 24\text{-h AMCV} = POD_{HEC} / (UF_H \times UF_D)$$

$$= 0.09\ mg/m^3 / (3 \times 1)$$

$$= 0.030\ mg/m^3$$

$$= 30\ \mu g/m^3 \text{ (rounded to two significant figures)}$$

Table 3 shows a summary of the derivation of the 24-h AMCV.

Table 3 Derivation of the Acute 24-h AMCV

Parameter	**Summary**
Study	Wilhelmsson and Holmstrom (1992)
Study population	66 exposed workers, 36 controls
Study quality	high
Exposure Methods	0.26 mg/m^3 for workers 0.09 mg/m^3 for controls
Critical Effects	elevated rates of symptoms such as eye, nasal, and lower airway discomfort
POD_{OC} (NOAEL)	0.09 mg/m^3
Exposure Duration	5 days per week, 10 years (mean)
Extrapolation to 24-h	Not applicable
24-h POD_{HEC}	0.09 mg/m^3
Total UFs	3
Interspecies UF	Not applicable
Intraspecies UF	3
LOAEL UF	Not applicable
Database UF *Database Quality*	1 High
Acute 24- h ReV **Acute 24-h AMCV**	**30 $\mu g/m^3$ (24 ppb)**

3.6 Values for Air Monitoring Evaluation

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

- 1-h acute health-based AMCV = 50 µg/m^3 (41 ppb) (TCEQ 2008)
- 24-h acute health-based AMCV = 30 µg/m^3 (24 ppb)
- 1-h acute odor-based AMCV = 620 µg/m^3 (500 ppb) (TCEQ 2008)

For the evaluation of 24-h ambient air monitoring data, the 24-h AMCV of 30 µg/m^3 (24 ppb) may be used for the evaluation of 24-h ambient air monitoring data (Table 1). 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 utilize 1-h and chronic (i.e., lifetime) health-protective and welfare-based (i.e., odor, vegetation) AMCVs.

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