Chlorine

CAS Registry Number: 7782-50-5

Prepared by
Shannon Ethridge, M.S., D.A.B.T.
Joseph T. Haney, Jr., M.S.
Toxicology Division

Development Support Document

Final, November 29, 2017

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

DSD History

Effective Date	Reason
July 29, 2011	Chlorine listed on public website as a chemical under consideration for ESL development
June 20, 2016	DSD proposed for public comment
November 29, 2017	DSD posted as final

TABLE OF CONTENTS

LIST OF TABLES

Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACC	American Chemistry Council
AEGL	Acute Exposure Guideline Level
AIC	Akaike's Information Criterion
ACGIH	American Conference of Governmental Industrial Hygienists
AIHA	American Industrial Hygiene Association
AMCV	Air Monitoring Comparison Value
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
$BMCL_{10}$	the lower 95% confidence limit on the benchmark concentration
BMDS	Benchmark Dose Software
^{o}C	degrees centigrade
DSD	development support document
EKG	electrocardiogram
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 effects
$^{chronic}ESL_{nonthreshold(nc)}$	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

Acronyms and Abbreviations	Definition
$^{chronic}ESL_{threshold(nc)}$	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
$FEF_{(25-75\%)}$	forced expiratory flow 25-75%
FEV_1	forced expiratory volume at 1.0 second
FIV	forced inspiratory volume
FVC	forced vital capacity
h	hour
HEC	human equivalent concentration
HQ	hazard quotient
HR	hyperresponsiveness
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
LOEL	lowest-observed-effect-level
MW	molecular weight
µg	microgram
$\mu g/m^3$	micrograms per cubic meter
MMF	maximal mid-expiratory flow
mg	milligrams
mg/m^3	milligrams per cubic meter
min	minute
MOA	mode of action
mmHg	millimeters of mercury
MRL	minimal risk level
n	number
N/A	Not applicable
NOAEL	no-observed-adverse-effect-level

Acronyms and Abbreviations	Definition
NRC	National Research Council
OEHHA	California Environmental Protection Office of Environmental Health Hazard Assessment
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
PVC	polyvinyl chloride
R_{aw}	airway resistance
REL	reference exposure level
ReV	reference value
RGDR	regional gas dose ratio
$RGDR_{ET}$	regional gas dose ratio for the extrathoracic region
SAR	seasonal allergic rhinitis
S_{raw}	specific airway resistance
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
TRRP	Texas Risk Reduction Program
TWA	time-weighted average
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
VC	vital capacity

Acronyms and Abbreviations	Definition
WHO	world health organization

Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation of chlorine, respectively, for use in air permitting and air monitoring. Please refer to the *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2015a) 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 chlorine's physical/chemical data.

Table 1. Acute Health and Welfare-Based Screening Values for Chlorine

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Acute ReV	1 h	140	50	N	none	--	Sensory irritation in humans.	
Acute ReV-24hr	--	--	--	--	--	--	--	--
^{acute}ESL [a]	**1 h**	**43**	**15**	**P**	**S,D**	**--**	**Same as above.**	--
^{acute}IOAEL	--	--	--	--	--	--	--	--
^{subacute}IOAEL	--	--	--	--	--	--	--	--
$^{acute}ESL_{odor}$	1 h	230	80	N	none	--	--	50% odor detection threshold.
$^{acute}ESL_{veg}$	2 h	290	100	N	none	--	Threshold for leaf injury in alfalfa and radish plant species.	--

Bold values used for air permit reviews; Chlorine is not monitored for by the TCEQ's ambient monitoring program.

[a] Based on the acute ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 2. Chronic Health and Welfare-Based Screening Values for Chlorine

Screening Level Type	Duration	Value 1 (µg/m³)	Value 2 (ppb)	Usage	Flags	Surrogated / RPF	Critical Effect(s)	Notes
Chronic $ReV_{threshold(nc)}$	70 yr	8.7	3.0	N	none	--	Ocular irritation and mild focal nasal and tracheal mucosal lesions in Rhesus monkeys	--
$^{chronic}ESL_{threshold(nc)}$ [a]	**70 yr**	**2.6**	**0.9**	**P**	**S,D**	**--**	**Same as above.**	--
$^{chronic}IOAEL_{(nc)}$	--	--	--	--	--	--	--	--
$^{chronic}ESL_{threshold(c)}$	--	--	--	--	--	--	--	Data are inadequate for an assessment of human carcinogenic potential.
$^{chronic}ESL_{nonthreshold(c)}$ [b]	--	--	--	--	--	--	--	--
$^{chronic}IOAEL_{(c)}$	--	--	--	--	--	--	--	--
$^{chronic}ESL_{veg}$	--	--	--	--	--	--	--	No relevant data found

Bold values used for air permit reviews

[a] Based on the chronic ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	Cl_2	ACGIH (2001)
Chemical Structure	Cl–Cl	TCEQ
Molecular Weight	70.91	ACGIH (2001)
Physical State at 25°C	Gas	ACGIH (2001)
Color	Greenish-yellow color at atmospheric pressure; amber liquid at -35ºC	ACGIH (2001)
Odor	Pungent, suffocating odor	ACGIH (2001)
CAS Registry Number	7782-50-5	ACGIH (2001)
Synonyms	Bertholite; hypochlorite; hypochlorous acid	Budavari et al. (1996) as cited in NRC (2004)
Solubility in water	Soluble, 7,000 mg/L @ 22°C	TRRP (2012)
Log K_{ow}	0.849	TRRP (2012)
Vapor Pressure	260 mm Hg @ 20°C	ACGIH (2001)
Relative Vapor Density (air = 1)	1.4085 @ 20°C and 6.864 atm (liquid)	ACGIH (2001)
Melting Point	-101°C	ACGIH (2001)
Boiling Point	-34.05°C @ 760 mm Hg	ACGIH (2001)
Conversion Factors	1 $\mu g/m^3$ = 0.344 ppb 1 ppb = 2.90 $\mu g/m^3$ at 25°C	ACGIH (2001)

Chapter 2 Major Sources and Uses

According to the American Chemistry Council (ACC):

Chlorine is used in a vast range of chemical processes to create thousands of products. While perhaps best known for its role in providing clean drinking water, chlorine chemistry also helps provide energy-efficient building materials, electronics, fiber optics, solar energy cells, pharmaceuticals, crop protection compounds, medical plastics, and much more. In most of these applications, there are no viable substitutes for chlorine.

Approximately 40% of chlorine produced in the United States is used to make polyvinyl chloride (PVC or vinyl) - a plastic found in such diverse products as prosthetic limbs and energy-saving windows. Another 37% of chlorine produced in North America is used to produce basic organic chemicals needed for manufacturing, and solvents for metalworking, dry cleaning, and electronics. Other large uses of chlorine include producing hydrochloric acid for myriad chemical processes and titanium dioxide, a white pigment.

As of 2009, approximately 117 facilities in Texas are dependent on chlorine or chlorine compounds (ACC 2010). Chlorine gas is not routinely monitored for in Texas. Facilities that emit chlorine gas, however, must comply with air permit limits and permitted levels should not cause short- or long-term adverse health or welfare effects.

Chapter 3 Acute Evaluation

The effects of acute chlorine inhalation exposure in humans and animals are reviewed extensively in ATSDR (2010) and NRC (2004). For purposes of this development support document (DSD), only a summary of relevant information is provided. Chlorine is an eye and respiratory tract irritant and at high doses has direct toxic effects on the lungs. Chlorine has the ability to reach the lungs at high exposure concentrations because it is only moderately soluble in water and is not totally absorbed in the upper respiratory tract at high concentrations. Human exposures at 30 ppm and 40-60 ppm were reported to cause intense coughing and serious damage (NRC 2004). Chlorine exposure in the range of 3-6 ppm results in stinging or burning sensations from irritation and corrosion of mucous membranes including the eyes, skin, and the respiratory system (Baxter et al. 1989, Wither and Lees 1985). Lower but still significant concentrations of chlorine can cause nasal congestion and irritation of the eyes, nose, and throat (e.g., see Section 3.1.2).

3.1 Health-Based Acute 1-Hour ReV and ^{acute}ESL

3.1.1 Physical Chemical Properties

Chlorine is extremely reactive and enters into substitution or addition reactions with both inorganic and organic substances. Moist chlorine unites directly with most elements. Reaction with water produces hydrochloric and hypochlorous acid (Budavari et al. 1996, Perry et al. 1994). Other relevant chemical and physical properties are listed in Table 3.

3.1.2 Key and Supporting Human Studies

Chlorine's irritant properties have been studied with human volunteers. Respiratory tract irritation is the adverse effect that occurs at the lowest concentration and is considered the critical effect. Five well-conducted human studies were available for review and are summarized in Table 4 (adapted from NRC 2004) and further described below.

3.1.2.1 Key Study (Anglen 1981)

Thirty-one human volunteers (ages 20-32 years) were exposed in an inhalation chamber to 0, 0.5, 1.0, or 2.0 ppm chlorine for 4 hours (h), or to 0.5 or 1.0 ppm chlorine for 8 h. The 8-h sessions were made up of two 4-h sessions separated by a 30- or 60-minute (min) lunch break during which the subjects were outside the chamber. Each subject filled out a questionnaire on subjective feelings of irritation upon entering the chamber and at 15, 30, 60, 90, 120, 180, and 240 min after entering. The same pattern was repeated during the second 4-h period in the case of an 8-h exposure. Subjects responded to a total of 14 questions using a scale of 0 to 5 (e.g., 0 = no sensation, 5 = unbearable).

Before entering the chamber, each subject's forced vital capacity (FVC) and forced expiratory volume at 1.0 second (FEV_1) was measured using a Collins survey spirometer. Additional measurements were made at 2 h into the 4-h session and at the end of the 4 h. In the case of the 8-h exposure, another measurement was taken at the end of the session. In some instances, subjects returned to the laboratory the next day for an additional test. A physician examined each subject's eyes before and after exposure and recorded any signs of irritation. While in the chamber, each subject exercised for 15 min/h.

Treatment of data for each sensation measured on the questionnaire included the calculation of the mean response for each combination of time and concentration. The mean response was then graphed versus time. An index of irritation was also calculated for each subject compiling scores for different sensations (excluding smell, taste, and shortness of breath).

In part one, subjective irritation levels of "just perceptible" to "distinctly perceptible" were reported at 0.5 ppm. Clear differences were observed between exposed subjects compared to controls for the irritant sensation of itching or burning of the throat after 1 h of exposure to 1

ppm chlorine. The differences between subjects exposed to 1 ppm for 1 h and controls were highly significant, even with responses greater than or equal to 3 (nuisance). The level of response was rated nuisance or greater at 2 ppm. Exposure to 0.5, 1, or 2 ppm did not result in pulmonary function changes. In part 2, exposure to 1 ppm for 8 h resulted in significant decreases in FVC and FEV_1 and increased subjective irritation. Consistent with assessments of the Anglen (1981) study conducted by the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA 1999), NRC (2004), and ATSDR (2010), the TCEQ considered 0.5 ppm to be a NOAEL and 1 ppm to be the LOAEL for sensory irritation without pulmonary function changes after 1 h of exposure. *The NOAEL of 0.5 ppm identified in this study for sensory irritation is used as the POD to derive the acute ReV.*

3.1.2.2 Supporting Human Studies

- Rotman et al. (1983), as a follow-up to the Anglen (1981) study, investigated the effects of chlorine inhalation exposure on eight healthy human volunteers (ages 19-33 years). All were nonsmokers and with the exception of one subject, had no history of respiratory disease and were "normal" on their physical examination within 1 week of exposure. Each subject served as their own control. On the day of exposure, each subject completed a series of pulmonary function tests. The subject then entered the exposure chamber and was exposed to either 0 (control), 0.5, or 1.0 ppm chlorine gas. Actual measured concentrations were 0, 0.45 ± 0.12 (mean ± standard deviation), and 0.95 ± 0.12. The subject remained in the chamber for 4 h, after which all pulmonary function tests were repeated outside the chamber before the subject reentered the chamber. After an additional 4 h of exposure, the subject again repeated all pulmonary function tests. The total test duration was 8 h. While in the chamber, each subject exercised for 15 min/h on an inclined treadmill or by a step test. Two hours after leaving the exposure chamber, the subject repeated the pulmonary function tests again, and again after 24 h from when the subject first entered the chamber. The function tests were then repeated daily until any persisting changes had returned to normal. The subject with a history of allergic rhinitis and indication of obstructive airway disease was the only one to experience severe distress during the exposure to 1 ppm and was unable to complete the full 8 h of exposure due to shortness of breath and wheezing. The atopic individual experienced several changes in pulmonary function parameters after exposure to chlorine at 0.5 ppm. The other (healthy) subjects reported itchy eyes, runny nose, and mild burning in throat after exposure to 1 ppm, but not 0.5 ppm or sham. For healthy subjects, pulmonary function test results (raw results) showed a decrease in FVC and FEV_1 at 1 ppm, but results were not as clear at 0.5 ppm. Airway function changes were dose- and duration-dependent, being more marked after 8 h than 4 h, and after 1 ppm than 0.5 ppm. The LOAEL for healthy human subjects was 1 ppm for a 4-h exposure for subjective symptoms of irritation (i.e., itchy eyes, runny nose, and mild burning in throat) as well as transient altered pulmonary function. This study identified a NOAEL of 0.5 ppm for healthy subjects. Although the atopic individual experienced slight irritation and transient slight

changes in pulmonary function at 0.5 ppm, this potential ≈2-fold difference in sensitivity will ultimately be more than accounted for through use of a full value of 10 for intrahuman variability in the acute ReV derivation process (see Section 3.1.7 below).

- D'Alessandro et al. (1996) investigated the effects of preexisting airway hyperresponsiveness on chlorine gas exposure response. Study subjects included healthy volunteers aged 18 to 50 years with and without baseline hyperreactivity defined by hyperresponsiveness (HR) to inhaled methacholine. Subjects were classified as having airway hyperreactivity if a nebulized dose of methacholine less than 8 milligrams per milliliter (mg/mL) induced a 20% or greater fall from baseline FEV_1. Twelve subjects participated in the study, seven were HR to methacholine and five were not. Five of the seven HR subjects had clinical histories of asthma, but only one was being treated regularly with inhaled or systemic corticosteroids. Chlorine was not appreciable by smell by any of the subjects at any of the exposure concentrations. Subjects were exposed to 0.4 or 1 ppm chlorine gas for 60 min. Subjects served as their own controls. Temperature and humidity were kept constant at 20ºC and 50%, respectively, throughout the study. Subjects were seated at rest during exposure. Subjects were coached to breathe at a rate of 20 liters per minute (L/min) through a mouth-breathing facial mask. Chlorine gas was diluted with humidified medical grade air to the desired concentration of either 0.4 or 1 ppm and mixed in a gas mixing chamber with 5% carbon dioxide to maintain isocapnea during hyperventilation. The chlorine concentration was monitored continuously throughout the exposure and maintained ±0.05 ppm of the target concentration. Subjects were tested for lung volumes, diffusing capacity, airway resistance (R_{aw}), and airway responsiveness to inhaled methacholine before and after exposure. Immediately after exposure to 1 ppm chlorine gas for 60 min, there was a statistically significant fall in FEV_1 and forced expiratory flow 25-75% (FEF_{25-75}) and a significant increase in specific airway resistance (S_{raw}) in both HR subjects and subjects without HR. There were no significant group changes in airflow, lung volumes, diffusing capacity, resistance, or methacholine responsiveness 24 h after exposure. Two HR subjects experienced unspecified "respiratory symptoms" following exposure to 1 ppm. When comparing HR subjects to subjects without HR, there was as statistically significant greater response to chlorine inhalation in the HR subjects as compared to the subjects without HR, measured by relative fall in FEV_1 or absolute increase in S_{raw}. By contrast, after asthmatic subjects were exposed at 0.4 ppm, there were no statistically significant changes in any pulmonary parameters either immediately following or 24 h after exposure. None of the subjects detected a chlorine odor at either exposure concentration. One limitation of the study is that subjects were not exposed to air alone (no chlorine) to determine if the experimental procedures had any effect on the measured parameters. This study identified a LOAEL of 1 ppm and a NOAEL of 0.4 ppm in asthmatics for airway responsiveness. This study was not selected as a key study because while the LOAEL was the same, the NOAEL was lower than the NOAEL identified in the key study.

- Shusterman et al. (1998) investigated the effects of chlorine gas exposure on a total of 16 human subjects. Each subject served as their own control and breathed either 0.5 ppm chlorine gas or clean air during 15-min exposure periods (1 week apart) using a nasal mask. Nasal airway resistance was documented by active posterior rhinomanometry perfomed before, immediately after, and 15 min after the exposure sessions. Equal numbers of subjects with seasonal allergic rhinitis (SAR) and nonrhinitic subjects were tested. The aim of the experiment was to test the hypothesis that subjects with SAR would exhibit a more marked physiologic response (congestion) to a given nasal irritant provocation than nonrhinitic subjects. Subjects with SAR experienced congestion to a significantly greater degree than did nonrhinitic subjects when chlorine and air conditions were compared immediately after, as well as 15 min after, provocation exposure. On a pooled basis (all subjects), statistically significant chlorine-related increases were apparent for mean ratings of nasal irritation and nasal congestion, although irritation was described as “none” to “slight.” No significant exposure-related changes were observed for rhinorrhea, postnasal drip, or headache, either on a pooled or stratified basis. Pulmonary peak flow tests showed that none of the subjects exhibited clinically significant changes in peak flow, nor did they complain of cough, wheezing, or chest tightness on chlorine exposure days. In addition, within either the SAR or non-SAR group, there was no relationship between subjective and objective congestion after chlorine exposure. Although increased nasal airway resistance was measured instrumentally in subjects with SAR, the subjects did not clearly perceive the effect as an adverse effect and ATSDR (2010) considered 0.5 ppm as the NOAEL for sensory irritation and pulmonary function based not only on this study but other acute database studies as well (e.g., Rotman et al. 1983, D’Alessandro et al. 1996).
- Joosting and Verberck (1974) exposed eight human subjects (ages 28-52) in an exposure chamber for 2 h to 0.5, 1, 2, and 4 ppm. Subjective reactions were noted every 15 min. Vital capacity (VC), FEV, and forced inspiratory volume (FIV) measurements before and after exposure showed no significant differences. At 0.5 and 1 ppm, all the group means were below the level of just perceptible, and the individual means figured below distinctly perceptible. At 2 ppm, the group means for smell, eye, nose, and throat irritation increased above the level of minimum perceptibility. At 4 ppm, irritation of the throat and coughing increased in intensity. All three subjects exposed to 4 ppm experienced the exposure as a limit due mainly to irritation of the throat. The LOAEL identified in this study was 2 ppm for 1-h exposure duration for eye, nose, and throat irritation. Individuals perceived the odor at 0.5 ppm after 15 min of exposure, although the odor perception intensity decreased over time.
- Schins et al. (2000) studied eight volunteers exposed to chlorine 6 h/day on 3 consecutive days to each of the four exposure conditions, 0, 0.1, 0.3, and 0.5 ppm chlorine. Pulmonary function including effort-dependent parameters and effort-independent parameters were evaluated before and after exposures. In addition, nasal lavage measurements were performed before and after each exposure and 1 and 4 days after each exposure. The nasal

lavage fluid was examined for total cells, epithelial cells, neutrophils, lymphocytes, eosinophils, monocytes, albumin (an indicator of epithelial permeability), and interleukin-8 (indicator of inflammatory response). Subjective complaints by the subjects were judged to be not treatment-related. Examination of the nasal lavages gave no indication of an inflammatory response or irritant effects on the nasal epithelium. The results of the pulmonary function tests showed that the only significant effect related to chlorine exposure was a difference in maximal mid expiratory flow (MMEF) between 0 and 0.5 ppm exposure; however, this was attributed to an unexplained shift in baseline values during control exposure (0 ppm) (ATSDR 2010). Thus, this 6 h/day, 3-day study provides support to 0.5 ppm as an acute NOAEL for pulmonary function, sensory irritation, and inflammatory response of the nasal epithelium.

Table 4. Summary of the Acute Irritant Effects of Chlorine in Humans [a]

Concentration (ppm)	Exposure Time	Effect	Study
0.4 (NOAEL)	1 h	No pulmonary function changes in subjects with airway hyperreactivity/asthma	D'Alessandro et al. (1996)
0.5 (NOAEL)	15 min	Statistically significant increase in nasal congestion, nasal irritation described as "none" to "slight" in rhinitic subjects exposed via nasal mask. No effects on nasal congestion in non-rhinitic subjects. No effects on pulmonary peak flow, rhinorrhea, postnasal drip, or headache in either type of subject	Shustermann et al. (1998)
0.5 (NOAEL)[b]	15 min-4 h; including the 1-h POD	Perception of odor, no discomfort, irritation effects reported as "just perceptible" to "distinctly perceptible," no changes in pulmonary function measurements for healthy individuals; some slight, transient, pulmonary function changes for atopic individual	Anglen (1981), Rotman et al. (1983)
0.5 (NOAEL)	6 h/day for 3 days	No effects on pulmonary function, sensory irritation, or inflammatory response of the nasal epithelium	Schins et al. (2000)
1.0 (LOAEL)	1 h	Statistically significant differences for respiratory tract irritation in subjects compared to controls; no significant changes in pulmonary function.	Anglen (1981)
1.0 (LOAEL)	1 h	Statistically significant but modest changes in pulmonary function measurements (FEV_1 and R_{aw}) for normal and asthmatic subjects	D'Alessandro et al. (1996)

Concentration (ppm)	Exposure Time	Effect	Study
1.0 (NOAEL)	2 h	Mean irritation of eyes, nose, and throat in healthy subjects below the level of "just perceptible"; no changes in pulmonary function	Joosting and Verberk (1974)
1.0 (LOAEL)	4 h	Transient changes in pulmonary function measurements (R_{aw})	Rotman et al. (1983)
1.0[c] (LOAEL)	8 h	Irritation (itchy eyes, runny nose, mild burning in throat); transient changes in pulmonary function measurements; atopic subject could not complete full 8-h exposure because of wheezing and shortness of breath	Anglen 1981, Rotman et al. (1983)
2.0 (LOAEL)	1 h	Itching or burning of throat, urge to cough at nuisance level	Anglen (1981)
2.0 (LOAEL)	2 h	Very slight irritation of eyes, nose, and throat in healthy subjects; no changes in pulmonary function	Joosting and Verbeck (1974)
2.0 (LOAEL)	4 h	50% response of subjects to sensations characterized as nuisance; itching or burning of nose or throat, urge to cough, runny nose, general discomfort; transient changes in pulmonary function	Anglen (1981)
2.0 (LOAEL)	8 h	Not immediately irritating, objectionable after several hours; increased mucous; transient changes in pulmonary function	Anglen (1981)
4.0 (LOAEL)	2 h	Nuisance level of throat irritation, perceptible to nuisance level of nose irritation and cough	Joosting and Verberk (1974)

[a] Table 4 is a reproduction of Table 1-3 in NRC (2004). Studies cited in this table include Anglen (1981) and Joosting and Verbeck (1974), which were performed in healthy adults. Studies conducted by Shusterman et al. (1998) and Rotman et al. (1983) included atopic individuals. D'Alessandro et al. (1996) was performed in both healthy subjects and asthmatic subjects.
[b] Point of departure used to derive the acute ReV.
[c] Eight-hour studies were composed of two segments with a 30-min or 1-h break after 4 h.

3.1.3 Consideration of Developmental/Reproductive Effects

Chlorine produces point-of-entry (POE) effects in the respiratory tract after inhalation exposure and significant systemic absorption does not occur at environmentally-relevant concentrations (NRC 2004). One study in humans evaluated the outcome of 15 pregnancies among female workers at a chlorine plant from 1932-1933, but did not provide any evidence of reproductive toxicity (Skjanskaya et al. 1935 as cited in ATSDR 2010). No other human inhalation studies

were found in the available literature. WHO (1982) reported that early studies in rabbits exposed to chlorine concentrations 0.6 to 1.6 ppm during pregnancy gave birth to healthy offspring.

Kutzman et al. (1983) exposed male and female rats intermittently to up to 5 ppm chlorine by inhalation for 62 days (d). At the end of the 62 d, male rats were mated with unexposed females, and 10 exposed females were mated with unexposed males. All female rats were sacrificed on gestation day 19 for the evaluation of reproductive endpoints. The results showed no significant effects of chlorine exposure on fertility, number of corpora lutea, viable embryos, early or late deaths, or pre-implantation losses. In the males exposed for 62 d, there were no histological alterations in the testes, and sperm morphology was unremarkable. The NOAEL identified in Kutzman et al. (1983) is 5 ppm for a 62 d exposure for lack of adverse effects on fertility of male and female rats and sperm morphology.

Systemic absorption and distribution of chlorine can occur following ingestion and the developmental/reproductive effects of chlorine ingestion have been studied (AIHA 1988, USEPA 1996). Ingestion exposure studies “demonstrated no or insufficient evidence of reproductive or developmental toxicity” (NRC 2004). As chlorine produces POE effects in the respiratory tract at inhalation LOAELs lower than the developmental/reproductive NOAELs discussed above and significant systemic absorption does not occur at environmentally relevant concentrations, an acute (and chronic) ReV protective of respiratory tract effects is expected to be protective of any potential developmental/reproductive effects.

3.1.4 Mode-of-Action (MOA) Analysis and Dose Metric

Chlorine is categorized as a Category 1 gas that rapidly and irreversibly reacts with the surface liquid and tissue of the respiratory tract, reacting with water to form hydrochloric acid (HCl) and hypochlorous acid (HClO) (NRC 2004). The latter spontaneously breaks down into HCl and free $O^{\cdot}$ that combines with water to release oxygen radicals (O^{-}). The oxygen radical produces major tissue damage, which is enhanced by the presence of HCl. At concentrations ≤ 2.5 ppm for up to 2 years of exposure, chlorine is effectively scrubbed in the anterior nasal passages. At concentrations > 2.5 ppm, chlorine is not effectively scrubbed in the upper respiratory tract and is capable of exerting its effects in the lower respiratory tract. As alluded to above, chlorine is corrosive and with surface liquids in the respiratory tract forms hydrochloric and hypochlorous acid, which can damage tissues of the respiratory tract. Additionally, the MOA for sensory irritation due to chlorine exposure involves stimulation of the trigeminal nerve endings in the respiratory mucosa (NRC 2004). Arts et al. (2006) state the free nerve endings of the trigeminal system innervate the walls of the nasal passages and eyes and respond with nasal pungency or watery/prickly eyes to a large variety of volatile chemicals.

As the air concentration of chlorine increases, it first causes a perception of odor intensity, then minor eye irritation followed by irritation to the respiratory tract. Chemical stimulation of the vagal or glossopharyngeal nerves may be involved as well as trigeminal stimulation for sensory irritation. Sensory and respiratory irritation, as well as any respiratory epithelial lesions which may develop, are threshold effects which may occur in tissues at sites where chlorine is deposited (i.e., points of contact). Because chlorine reacts and exerts effects at the POE and there is insignificant distribution remote to the respiratory tract, remote systemic effects (e.g., developmental/reproductive effects) are not expected at environmentally-relevant concentrations.

In the key study, data on exposure concentration of the parent chemical are available and will be used as the dose metric.

3.1.5 Critical Effect and Point of Departure (POD) for the Key Study

In the key study by Anglen (1981), exposure concentrations of 1 ppm and above after 1 h caused "nuisance" levels of irritation. Pulmonary function changes were observed in subjects exposed to 1 ppm chlorine for 8 h. Consistent with evaluation of the acute database by ATSDR (2010), the TCEC considers 0.5 ppm to be the acute NOAEL for chlorine-induced sensory irritation. This 1-h NOAEL will be used to derive the acute ReV.

3.1.6 Adjustments of the POD

3.1.6.1 Exposure Duration Adjustment

Data suggest the response to chorine-induced irritation is concentration- rather than time-dependent (NRC 2004). Regardless, since the Anglen (1981) study identified a NOAEL of 0.5 ppm for a 1-h exposure duration, no duration adjustment was necessary to convert the POD to a 1-h concentration POD_{ADJ} (TCEQ 2015a).

3.1.6.2 Dosimetric Adjustment

The Anglen (1981) study was conducted in humans. Therefore, a dosimetric adjustment was not necessary to determine the human equivalent concentration POD (POD_{HEC}). The POD_{HEC} is 0.5 ppm

3.1.7 Adjustments of the POD_{HEC}

Sensory irritation is a threshold effect. Therefore, the POD_{HEC} was divided by relevant uncertainty factors (UFs) to derive the acute ReV (TCEQ 2015a). The following UFs were applied to the POD_{HEC} of 0.5 ppm: 10 for intrahuman variability (UF_H) and 1 for database uncertainty (UF_D), for a total UF of 10:

- a UF_H of 10 was conservatively used for intrahuman variability to protect potentially sensitive subpopulations (e.g., people with pre-existing health conditions such as airway hyper-reactivity or asthma). Although the POD used to derive the acute ReV is considered a NOAEL, there is some evidence that sensitive humans begin to experience mild effects of chlorine exposure at 0.5 ppm; therefore, a full UF_H of 10 was used. Note that this is 8 times more conservative than using the NOAEL of 0.4 ppm identified in a sensitive subpopulation (i.e., asthmatics in D'Alessandro et al. 1996) without the need of a UF_H greater than 1, and is 5 times more conservative than using a potential minimal LOAEL of 0.5 ppm for sensitive subpopulations (e.g., increased nasal congestion in subjects with SAR in Shusterman et al. 1998; an atopic individual experienced slight irritation and transient slight changes in pulmonary function at 0.5 ppm in Rotman et al. 1983) with a UF_L of 2 but without the need of a UF_H greater than 1.
- a UF_D of 1 was used since the overall acute database is considered to be of high confidence. There are a number of well-conducted studies available that evaluate the acute effects of chlorine inhalation in humans and animals. As a result, the effects of acute exposure of humans and animals to chlorine are well characterized, with the animal database being particularly extensive. Furthermore, probably because chlorine is highly reactive and exerts effects at the POE with insignificant distribution remote to the respiratory tract, it has not been demonstrated to cause reproductive or developmental effects at any dose, much less at environmentally-relevant concentrations, nor would such effects be expected. A UF_D of 1 is consistent with TCEQ (2015a) as well as ATSDR's determination that reliable and sufficient data exist to identify the most sensitive health effect(s) due to exposure to airborne chlorine (ATSDR 2010).

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_D)$$

$$= 0.5 \text{ ppm} / (10 \times 1)$$
$$= 0.05 \text{ ppm}$$
$$= 50 \text{ ppb (rounded to two significant figures)}$$

3.1.8 Health-Based Acute ReV and ^{acute}ESL

The acute ReV of 50 ppb was rounded to two significant figures at the end of all calculations resulting in a value of 50 ppb. The acute ReV of 50 ppb (140 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 15 ppb (43 µg/m^3) (Table 5).

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

Parameter	Values and Descriptions
Study	Anglen (1981)
Study Population	31 human volunteers (ages 20-32 years)
Study Quality	Medium to High
Exposure Methods	Inhalation chamber to 0, 0.5, 1, or 2 ppm chlorine gas for 15 min to 8 h
POD_{HEC}	0.5 ppm, NOAEL
Critical Effects	Sensory irritation
Exposure Duration	1 h
Total UFs	10
Intraspecies UF	10
Incomplete Database UF Database Quality	1 High
acute ReV [1 h] (HQ = 1)	**50 ppb (140 µg/m^3)**
^{acute}ESL [1 h] (HQ = 0.3)	**15 ppb (43 µg/m^3)**

3.1.9 Comparison of Acute ReV to Other Acute Regulatory Values

The acute ReV is slightly lower than the California OEHHA reference exposure level (REL) of 72 ppb (OEHHA 1999), which is based on Anglen (1981) and is protective of an exposure up to 1 h. The acute ReV is also slightly lower than the ATSDR acute inhalation minimal risk level (MRL) of 60 ppb (ATSDR 2010), which is considered protective of up to 14 days of exposure and is based on a NOAEL of 0.5 ppm for sensory irritation and pulmonary effects in volunteers exposed for up to 8 h/d (Anglen 1981, D'Alessandro et al. 1996, Rotman et al. 1983, Schins et al. 2000, Shusterman et al. 1998, 2003).

Lastly, it is noted that the acute ReV for chlorine (Cl_2) of 140 µg/m^3 is within a factor of 5 of (i.e., 4.6-fold lower than) the acute ReV for HCl on a chlorine content basis (i.e., HCl acute ReV of 660 µg/m^3 × MW of Cl/MW of HCl = 660 µg/m^3 × 35.45/36.46 = 642 µg/m^3 as Cl; TCEQ 2015c). This is a reasonable difference considering, for example, that the original authors of the different studies selected the exposure concentrations that ultimately determined the study PODs (i.e., NOAELs) in both cases and that the values of UFs used to reduce PODs are generally limited to factors of 3 and 10. Similar to the difference between the TCEQ acute ReV for chlorine versus that based on the chlorine content of HCl, the acute exposure guideline levels (AEGL-1 values for nondisabling effects) for chlorine and HCl show reasonably good agreement. That is, the

AEGL-1 for chlorine (500 ppb) is within a factor of 4 of (i.e., 3.5-fold lower than) the AEGL-1 for HCl on a chlorine content basis (i.e., HCl AEGL-1 of 1,800 ppb × MW of Cl/MW of HCl = 1,800 ppb × 35.45/36.46 = 1,750 ppb as Cl; NRC 2004).

3.2 Health-Based Acute 24-Hour ReV

Texas does not monitor the air for chlorine. Therefore, a 24-h ReV is not needed and was not derived.

3.3 Welfare-Based Acute ESLs

3.3.1 Odor Perception

Chlorine has a pungent, irritating, bleach-like suffocating odor with a wide odor detection threshold range of 21 to 3,400 ppb (AIHA 1989). Nagata (2003) reported a 50% odor detection threshold of 1,500 ppb using the triangular bag method. The detection threshold reported by Dixon (1977) was 80 ppb. Amoore and Hautala (1983) and Leonardos et al. (1969) reported a 100% odor detection threshold for chlorine of 310 ppb.

Based on a weight of evidence approach and historical information, the $^{acute}ESL_{odor}$ value was set at 80 ppb (230 µg/m^3) (TCEQ 2015b). Because odor is a concentration-dependent effect, the same 1-h $^{acute}ESL_{odor}$ can be assigned to all averaging time durations for air monitoring sampling and/or air dispersion modeling results.

3.3.2 Vegetation Effects

Numerous studies evaluating the effects of chlorine gas exposure on vegetation have been conducted following accidental chlorine gas releases or have been conducted in a controlled environment (Schreuder and Brewer 2001). According to Schreuder and Brewer (2001), "the most common foliar injury symptoms after exposure to chlorine gas include chlorosis (bleaching of tissues), necrotic mottling (red and black dark spots on the leaf surface), and necrosis (death of cells and cell tissue)." Adverse vegetation effects can occur in both deciduous and coniferous species. Toxicity thresholds are dependent on plant species, duration of exposure, and stomatal conductance (Brennan et al. 1965, Griffiths and Smith 1990). Chlorosis and necrosis have been reported after exposure to chlorine concentrations as low as 0.5 to 3 ppm.

Studies evaluated in the acute assessment of chlorine gas exposure are listed below:

- Brennan et al. (1965) investigated the effects of 0.1 to 1.5 ppm chlorine gas exposure on many plant species. Concentrations of 0.1 to 1.5 ppm for up to 4 h produced a variety of adverse effects, resulting in the development of bleaching and necrosis. Low soil moisture levels were associated with decreased incidence of injury. The most sensitive species were

radish and alfalfa, showing adverse effects after exposure to 0.1 ppm chlorine for 2 h. All other species tested showed effects at higher chlorine concentrations.

- Zimmerman (1955) exposed 19 species of plants to chlorine at concentrations ranging from 0.46 to 4.67 ppm for durations of 20 to 480 min. Sixteen species were found to be susceptible. The plant material took on a cooked appearance and finally turned a straw/brown colour depending upon the species. Medium to considerable injury was associated with leaf fall.
- Benedict and Breen (1955) studied the effects of chlorine exposure on different types of weeds. Plants were exposed to 0.5 and 2.5 ppm chlorine under high and low soil moisture conditions for 4 h. Broad-leaved species developed marginal streaks which progressed to the main vein in the region between the tip and the point where the leaf bends. Mustard, chickweed, and sunflower were the most sensitive species. Low soil-moisture levels were associated with decreased sensitivity to chlorine.
- Thornton and Setterstrom (1940) exposed plants to chlorine gas concentrations of 1, 4, 16, 63, 250, and 1,000 ppm for 1, 4, 15, 60, 240, and 960 min. Adverse effects were both concentration- and time-dependent and the response was greater in clear weather (verses cloudy). Leaf injury was the most sensitive endpoint evaluated in this study. The dose-response curve for leaf injury was very steep at the highest chlorine concentrations tested. Sixty ppm chlorine gas caused 50% leaf injury after approximately 1 min of exposure and 4 ppm chlorine gas caused 50% injury of the leaf area after approximately 10 min of exposure. Based on the time-concentration curve, we estimate that 1 ppm chlorine gas exposure for approximately 1 h would cause 50% leaf injury. All concentrations tested caused an effect so a threshold could not be determined.

According to TCEQ Guidelines (2015a), the vegetation-based ESL should be set at the lowest-observed effect level (LOEL). Based on the studies evaluated, the LOEL identified was 0.1 ppm chlorine gas after 2-h exposure to radish and alfalfa in Brennan et al. (1965). Therefore, the vegetation-based ESL is 0.1 ppm (100 ppb, 290 µg/m^3).

3.4 Short-Term ESL and Values for Air Monitoring Evaluation

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

- acute ReV = 140 µg/m^3 (50 ppb)
- ^{acute}ESL = 43 µg/m^3 (15 ppb)
- $^{acute}ESL_{odor}$ = 230 µg/m^3 (80 ppb)
- $^{acute}ESL_{veg}$ = 290 µg/m^3 (100 ppb)

For the evaluation of any ambient air monitoring data, the acute ReV is lower than the $^{acute}ESL_{odor}$ (Table 1), although both values may be used for the evaluation of air monitoring data from a human health perspective. The short-term ESL for air permit evaluations is the health-

based ^{acute}ESL of 43 µg/m^3 (15 ppb) as it is lower than the odor- and vegetation-based ESLs (Table 2). The ^{acute}ESL (HQ = 0.3) is not used to evaluate any ambient air monitoring data and will be used in air permitting applications.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Chlorine gas has been used in industrial processes for many years and several occupational studies have been published. Additionally, several long-term controlled inhalation exposure studies have been conducted in animals. A detailed assessment of all available long-term inhalation human and animal studies can be found in ATSDR (2010). For purposes of this DSD, only a summary of relevant information is provided.

4.1.1 Key and Supporting Studies

4.1.1.1 Human Studies

Although several occupational studies are available, none of them are suitable for the derivation of a chronic inhalation toxicity factor (ATSDR 2010). However, brief descriptions are provided below.

- Kennedy et al. (1991) compared 321 pulp mill workers (189 were exposed to chlorine or chlorine dioxide "gassings") to a control group of 237 rail yard workers in similar working conditions but not exposed to chlorine. The pulp mill workers had been employed for an average of 13 years. The rail yard workers had been employed for an average of 12.7 years. Chlorine gas and chlorine dioxide levels were measured together over a 4-week period during mainly during a 12-h shift. Time weighted averages (TWAs) were < 0.1 ppm, with the highest < 0.1-0.3 ppm. A significantly higher prevalence of wheezing was observed in pulp mill workers who had reported more than one episode of chlorine gassing as compared to controls. Workers had more airflow obstruction, correlating to significantly lower average values for maximal mid-expiratory flow (MMF) and for the FEV_1 to FVC ratio. Results from this study suggest that chronic respiratory health impairment is associated with chronic, repeated exposure to chlorine and/or chlorine dioxide. The authors hypothesized that an inflammatory response occurred in small airways after the first high exposure to chlorine and/or chlorine dioxide, and this reaction did not resolve in workers who were continuously or repeatedly exposed to the irritant. Study results also suggest that chronic airflow obstruction caused by repeated minor exposures led to chronic respiratory disability in some of the workers. One major limitation of this study was that subjects were exposed to other compounds along with chlorine, so the adverse effects experienced by workers could not be attributed solely to chlorine. Also, workers were exposed to multiple acute

"gassings" (OEHHA 2000a), and other confounding variables like smoking were not accounted for. Due to the potential confounding variables, Kennedy et al. (1991) was not used to derive the chronic ReV.

- Shi et al. (1990) evaluated 353 workers from a diaphragm cell chlorine chemical plant. The average age of workers was 42.4 years (ranging from 23-52 years). Workers were split into two groups. Group A was comprised of 220 workers who had been employed/exposed for 10-25 years, while Group B was comprised of 133 workers employed/exposed for less than 10 years. Both groups of workers were exposed to a range of 2.60 to 11.0 mg/m^3 (0.37 to 1.75 ppm) chlorine. The control group was comprised of 192 workers not exposed to chlorine, with an average age of 39.7 years (ranging from 26-55 years). All participants were subjected to a clinical examination, ear/nose/throat examination, chest x-rays, pulmonary function tests, and were evaluated for respiratory symptoms and smoking habits. Groups A and B showed a 3-8 times higher incidence of upper airway complaints (e.g., sore throat, hoarseness, dryness in the throat and respiratory symptoms such as shortness of breath, chest tightness, chest tightness and pain, wheezing, cough, and phlegm) than the control group. Current smokers in Groups A and B experienced the highest incidence of pulmonary symptoms and Group A workers had a higher prevalence of rhino-pharyngeal signs than the control workers. Abnormalities in chest x-rays were seen in 8.6% of Group A workers and in 2.8% of Group B workers, compared to 2.3% of controls. Groups A and B showed significantly impaired pulmonary function in tests (e.g., FEF_{25-75}) compared to controls. Group A showed reduced FEV_1 results compared to controls. Exposed workers experienced a number of symptoms at a higher prevalence than controls. In addition, the prevalence of several effects was higher in workers with a long duration of exposure (> 10 years) than in workers with a shorter duration of exposure. Adverse effects were noted in workers exposed for less than 10 years, and more severe effects were observed in workers exposed for more than 10 years. Although this study was relatively well-conducted and examined a number of endpoints, the exposure concentration estimates had a high degree of uncertainty; therefore, it was not used to develop the chronic ReV.
- Enarson et al. (1984) compared 392 pulp mill workers exposed to chlorine to a comparable group of 310 rail yard workers living in the same community, but not exposed to chlorine. Pulp mill workers were exposed to an average of 0.02 ppm (machine room) or 0.18 ppm (bleach plant) chlorine. Other possible exposures included sulfur dioxide, hydrogen sulfide, and methylmercaptan, in addition to various particulates (ATSDR 2010). Approximately 23% of machine room workers experienced cough, as did 32.8% of bleach plant workers, compared to 22.3% of controls. Chest tightness occurred in 31.5% of the machine room workers and 39.6% of the bleach plant workers, compared to 21.3% of controls. Only data from Caucasian subjects were reported. As indicated by ATSDR (2010), given the small number of workers involved, the possibility of exposure to multiple chemicals, and the lack of information on chlorine peak exposure levels, the validity of the 0.18 ppm as an effect

level is questionable. The TCEQ concurs and consequently, this study was not used to derive the chronic ReV.

- Patil et al. (1970) studied the health effects of chlorine inhalation exposure in 600 workers from 25 plants producing chlorine in North America. The control group consisted of workers who were not routinely exposed to chlorine. The average duration of exposure was 11.9 years. Tobacco and alcohol use were monitored and each worker received a physical exam which included evaluation of medical and occupational histories. The chlorine concentration was monitored every two months for a period of one year in certain areas, but no other details were given. Exposure data were available for 332 workers and showed a TWA 8-h mean of 0.15 ± 0.29 ppm (range, 0.006 - 1.42 ppm). Most workers were exposed to less than 1 ppm, 94% were exposed to ≤ 0.5 ppm, and 70% were exposed to ≤ 0.2 ppm. Ninety-eight of the exposed workers were found to have abnormal teeth and gums, but no dose-response relationship could be determined. No dose-response relationship could be determined from other endpoints evaluated including symptoms of sputum production, cough, dyspnea, history of frequent colds, palpitation, chest pain, VC, maximum breathing capacity, forced expiratory volume. No significant difference was found between the exposed group and controls for other endpoints (i.e., electrocardiogram (EKG) abnormalities). No neurological defects, prolonged anoxia, gastrointestinal trouble, or abnormal incidence of dermatitis were noted. Exposed workers showed elevated white blood cell levels and decreased hematocrit values compared to controls. In summary, none of the endpoints examined showed a dose-response relationship and while the mean concentration of 0.15 ppm may be considered the study NOAEL, limitations such as unclear analytical methodology, no clear definition of the case/control populations, and insufficient detail regarding the method of analysis render the NOAEL questionable and preclude its use in development of the chronic inhalation toxicity factor (ATSDR 2010; OEHHA 2000a also notes highly variable exposures).
- Chester et al. (1969) evaluated 139 workers occupationally exposed to < 1 ppm chlorine. However, 55 of the 139 workers were accidentally exposed to high concentrations of chlorine, which were severe enough to require oxygen therapy. Ventilation was affected by chlorine inhalation with a decrease in the maximal MMF. MMF is thought to be the first ventilation function affected in obstructive airway disease. Fifty-six of the 139 subjects showed abnormal posteroanterior chest films, 49 of which had parenchyma and/or hilar calcifications consistent with old granulomatous disease and 11 of which had multiple, bilateral and diffuse calcifications. Limitations of this study preclude its use (e.g., high incidence of accidental exposures to high concentrations severe enough to require oxygen therapy, exposure duration unspecified).
- Ferris et al. (1967) evaluated the effects of chlorine exposure in pulp mill workers. A total of 147 workers and 124 controls were evaluated in the study and no significant difference was found in respiratory symptoms or in tests for FVC or FEV_1 between exposed and control groups. The study did not provide details on the duration of exposure or accurate

measurements of actual exposure concentrations. The same cohort was evaluated 10 years later and did not reveal an increase in mortality or increase in specific cause of death among exposed workers.

4.1.1.2 Animal Studies

Two high quality long-term animal inhalation studies have been conducted: Klonne et al. (1987) and Wolf et al. (1995). These studies are discussed below.

4.1.1.2.1 Key Animal Study (Klonne et al. 1987)

Klonne et al. (1987) conducted a one-year inhalation toxicity study of chlorine gas in Rhesus monkeys. Male and female monkeys (4/sex/exposure level) were exposed to 0, 0.1, 0.5, or 2.3 ppm chlorine 6 h/d, 5 d/week for 1 year. Pulmonary diffusing capacity of CO and distribution of ventilation, body weights, urinalysis, EKG, hematology, and clinical chemistry were evaluated monthly in the study. At termination, the heart, lungs, trachea, liver, gonads, kidneys, spleen, and brain were weighed. Results were compared to the same test measurements recorded prior to the study. No significant difference was seen in body weight at any point in the experiment. No exposure-related differences were seen in pulmonary function, neurologic examinations, EKGs, clinical chemistry, urinalysis, hematology, blood gas levels, or organ weights.

Monkeys exposed to 2.3 ppm experienced ocular irritation (tearing, rubbing of the eyes, reddened eyes) during the daily exposures after approximately 6 weeks of exposure, with some conjunctival irritation and some exudation at the end of the study. The only treatment-induced histopathological changes were found in the respiratory epithelium of the nasal passages and trachea and were limited to focal, concentration-related epithelial hyperplasia in the absence of epithelial thickening with loss of cilia and decreased numbers of goblet cells in affected areas. These changes were mild and focal and occurred in some monkeys of the 2.3 ppm exposure group. More specifically, 50% of the male and female monkeys exposed to 2.3 ppm had mild nasal mucosal lesions and 50% of the females had mild tracheal mucosal lesions. Small zones of respiratory epithelium in affected areas of the nasal passages (most commonly in the angular margins of the turbinates) exhibited hypercellularity with loss of goblet cells and cilia. Only trace, less distinct respiratory epithelial lesions were observed in the nose at lower chlorine concentrations (≤ 0.5 ppm). These changes at ≤ 0.5 ppm were very minimal and were confined to the nasal passages of some treated monkeys and one male control animal. Moreover, the biological significance/adversity of these lesions is questionable. For example, while extensive areas of deciliation in the nasal passages of rats impairs mucociliary function in affected regions of the nose, an effect relevant to airway clearance and adversity considerations, mucus may continue to flow over small, limited areas of impaired ciliary function as observed in this study. Consequently, the limited nature of the effects at ≤ 0.5 ppm does not appear to meet the USEPA definition of an adverse effect as “any effect resulting in functional impairment and/or

pathological lesions that may affect the performance of the whole organism, or that reduce an organism's ability to respond to an additional challenge" (USEPA 1994). Additionally, exposure to ≤ 2.3 ppm did not induce any pulmonary effects (e.g., lesions), much less any indicative of potential impairment of pulmonary defenses. Consistent with the above discussion, 2.3 ppm is considered the LOAEL for ocular irritation and mild focal nasal and tracheal mucosal lesions, while 0.5 ppm is considered the LOEL for less distinct trace changes considered less than adverse. Although this study did not use 1 ppm as an exposure concentration, it is noted that exposure of Rhesus monkeys to 1 ppm would have likely also produced effects such as sensory irritation similar to those shown in humans following shorter-term exposure to 1 ppm (e.g., Anglen 1981, Rotman et al. 1983). *The LOEL of 0.5 ppm will be used to derive the chronic ReV.*

4.1.1.2.2 Supporting Animal Study (Wolf et al. 1995)

Wolf et al. (1995) exposed male and female B6C3F1 mice and F344 rats to chlorine gas concentrations of 0, 0.4, 1.0, and 2.5 ppm for 2 years. Female rats were exposed for 6 h/d, 3 d/week and mice and male rats were exposed for 6 h/d, 5 d/week. Treatment groups contained 320 male and 320 female mice. Rats were studied in groups of 70. For the first 13 weeks of observation, body weights and clinical observations were noted weekly, and for the remainder of the study, they were recorded once every two weeks. After 52 weeks, 10 rats were euthanized and autopsied. Organ weights were recorded, and hematological and clinical chemistry parameters were determined. The same measurements were performed on all surviving mice and rats at the end of the experiment. Male mice exposed to 1.0 and 2.5 ppm chlorine showed decreased weight gain compared to controls while only female mice exposed to 2.5 ppm showed decreased weight gain. Male rats showed decreased weight gain at all levels of exposure while female rats showed the same result at only 1.0 and 2.5 ppm chlorine exposures. Various non-neoplastic nasal lesions were seen in all the airway epithelial types in the nose and at all levels of exposures for both species. These lesions were evaluated against background lesions found in the control animals. A statistically significant incidence of fenestration was seen in all three exposure concentrations of chlorine. Statistically significant responses were seen in the transitional and respiratory epithelial regions of all exposed rats and mice. Statistically significant damage to olfactory epithelium occurred in all exposed rats and female mice as well as in male mice exposed to 1.0 and 2.5 ppm chlorine. The LOAEL identified in this study was determined to be 0.4 ppm for non-neoplastic nasal lesions in both rats and mice.

In regard to the relevance of rodent versus primate animal models for use in dose-response assessment for human health, ATSDR (2010) indicates [*emphasis added*], "For the most part, monkeys exhibited only mild concentration-related respiratory epithelial hyperplasia with focal loss of cilia over the range of concentrations tested (0, 0.1, 0.5, and 2.3 ppm) and showed no evidence of the major nasal lesions seen in rats and mice. These differences are probably related to species-specific respiratory-tract airflow characteristics (Ibanes et al. 1996), which in

turn, are determined by anatomical differences. Moreover, rats and mice are obligatory nose breathers with a greater surface-area-to-volume ratio of the upper respiratory tract than primates. Therefore, exposure of rodents and primates to equal concentrations for equal amounts of time will likely result in greater pathological changes in the nasal area of the rodent (Barrow et al. 1979). *It appears, therefore, that primates are a better model to evaluate potential respiratory effects in humans than rodents*. For these reasons, the study in monkeys (Klonne et al. 1987) was selected for deriving a chronic-duration inhalation MRL for chlorine." For the same reasons, the study in monkeys by Klonne et al. (1987) was selected by the TCEQ for derivation of the chronic ReV.

4.1.2 Consideration of Developmental/Reproductive Effects

In long-term exposure duration studies, exposure of male and female monkeys for 1 year or male and female rats and male mice for 2 years up to 2.5 ppm chlorine did not result in gross or microscopic alterations of the reproductive organs (Klonne et al. 1987, Wolf et al. 1995). See Section 3.1.3 for additional information on the findings of developmental/reproductive studies. Moreover, since chlorine produces POE effects in the respiratory tract after inhalation exposure and significant systemic absorption does not occur at environmentally relevant concentrations, a chronic ReV protective of respiratory tract effects is expected to be protective of any potential developmental/reproductive effects.

4.1.3 MOA Analysis

As in the case of acute exposure to chlorine gas, the most sensitive effects due to long-term exposure occur in the upper respiratory tract. At concentrations ≤ 2.5 ppm for up to 2 years of exposure, chlorine is effectively scrubbed in the anterior nasal passages. As a category 1 gas, chlorine rapidly and irreversibly reacts with the surface liquid and tissue of the respiratory tract (NRC 2004). See Section 3.1.4 for additional information relevant to the MOA.

4.1.4 Dose Metric

In the key study by Klonne et al. (1987), data on exposure concentration of the parent chemical are available. Therefore, exposure concentration of the parent chemical will be used as the default dose metric in the absence of data on other more specific dose metrics.

4.1.5 Critical Effect and POD for Key Study

In the key study by Klonne et al. (1987), ocular irritation and mild focal nasal and tracheal mucosal lesions occurred in Rhesus monkeys exposed for 1 year to chlorine gas at the LOAEL of 2.3 ppm. These are considered the long-term critical effects. The LOEL of 0.5 ppm was associated with trace changes considered less than adverse and will be used as the POD to derive the chronic ReV.

4.1.6 Adjustments of the POD

4.1.6.1 Exposure Duration Adjustment

The POD of 0.5 ppm was obtained from an animal study in which Rhesus monkeys were exposed to chlorine gas 6 h/d, 5 d/week for 1 year (Klonne et al. 1987). NRC (2004) indicates that time-scaling is relevant for chlorine-induced tissue damage. Since the animals were not exposed continuously, the POD was adjusted to a continuous exposure concentration using the following dosimetric adjustment calculation:

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

where: POD_{ADJ} = POD from an animal study, adjusted to a continuous exposure duration
POD = POD from an animal study, based on a discontinuous exposure duration
D = exposure duration, h/d
F = exposure frequency, d/week

$$POD_{ADJ} = 0.5 \text{ ppm} \times 6/24 \times 5/7$$
$$POD_{ADJ} = 0.0893 \text{ ppm}$$

4.1.6.2 Dosimetry Adjustment from Animal-to-Human Exposure

A dosimetric adjustment from an animal concentration to a human equivalent concentration (POD_{HEC}) was performed for chlorine, a category 1 gas producing respiratory effects in the extrathoracic (ET) region (includes the nasal and oral passages, pharynx, and larynx). Dosimetric adjustments were performed as a Category 1 gas based on updated animal-to-human dosimetric recommendations in USEPA (2012). The default regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) is 1.

$$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$$
$$= 0.0893 \text{ ppm} \times 1$$
$$= 0.0893 \text{ ppm}$$
$$= 89.3 \text{ ppb}$$

The resulting POD_{HEC} is 89.3 ppb.

4.1.7 Adjustments of the POD_{HEC}

The critical long-term effects identified in Klonne et al. (1987) are ocular irritation and mild focal nasal and tracheal mucosal lesions. Since these are threshold effects, the POD_{HEC} was

divided by relevant UFs to derive the chronic ReV (TCEQ 2015a). The following UFs were applied:

- a UF_H of 10 was applied to account for human variability and potentially sensitive subpopulations (e.g., children, the elderly, individuals with pre-existing conditions).
- a UF_A of 1 was used for animal-to-human variability because a dosimetric adjustment has already been performed and toxicodynamics (TD) are expected to be similar for the critical effects considering: (a) nonhuman primates are the most suitable animal models to evaluate the potential respiratory effects of chlorine in humans (e.g., see the end of Section 4.1.1.2.2); (b) nonhuman primates reflect key features of human lung architecture and the overall pattern of conducting airway epithelial differentiation is similar in Rhesus monkeys and humans (Phillips et al. 2014); (c) in addition, intranasal airflow patterns play a major role in determining where toxicant-related lesions may occur and air flow patterns show great similarity between monkeys and humans due to similar nasal gross anatomy (Harkema et al. 2006); (d) phylogenetic similarities; and (e) the MOA involves chlorine directly reacting with and damaging POE tissues of the respiratory tract to induce nasal epithelial lesions. Thus, both the stated similarities between nonhuman primates and humans as well as the MOA for the chlorine-induced critical effects provide support for an expectation of similar nasal response (e.g., potential for lesions) in monkeys and humans.
- a UF_{sub} (subchronic-to-chronic UF) value of 3 was used because although the study duration was 1 year, which is usually considered chronic for a laboratory animal study (e.g., ATSDR 2010 considers it chronic), this duration is less than 10% of the average lifespan of a Rhesus monkey (≈35 years) so a UF_{sub} is considered (TCEQ 2015a).
- a UF_D of 1 was used because the database for chlorine is one of high confidence. There are long-term toxicity data for three species (i.e., rats, mice, monkeys) in well-conducted studies examining numerous endpoints. Furthermore, probably because chlorine is highly reactive and exerts effects at the POE with insignificant distribution remote to the respiratory tract, it has not been demonstrated to cause reproductive or developmental effects at any dose, much less at environmentally-relevant concentrations, nor would such effects be expected. A UF_D of 1 is consistent with TCEQ (2015a) as well as ATSDR's determination that reliable and sufficient data exist to identify the most sensitive health effect(s) due to exposure to airborne chlorine (ATSDR 2010).

A total UF of 30 was applied to the POD_{HEC} of 89.3 ppb to derive the chronic ReV of 4.5 ppb (rounded to two significant figures):

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

$$= 89.3 \text{ ppb} / (10 \times 1 \times 3 \times 1)$$
$$= 89.3 \text{ ppb} / 30$$

= 2.97 ppb
= 3.0 ppb (rounded to two significant figures)

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

The chronic ReV value was rounded to the least number of significant figures for a measured value at the end of all calculations. Rounding to two significant figures, the chronic ReV is 3.0 ppb (8.7 µg/m^3). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 0.9 ppb (2.6 µg/m^3) (Table 6).

Table 6. Derivation of the Chronic ReV and $^{chronic}ESL$

Parameter	Values and Descriptions
Study	Klonne et al. (1987)
Study Population	32 Rhesus monkeys (4/sex/exposure level) were exposed to 0, 0.1, 0.5, or 2.3 ppm chlorine gas
Study Quality	High
Exposure Method	Inhalation
Critical Effects	Ocular irritation and mild focal nasal and tracheal mucosal lesions
POD (LOEL)	500 ppb
Exposure Duration	6 h/d, 5 d/week, for one year
Extrapolation to continuous exposure (POD_{ADJ})	89.3 ppb
POD_{HEC}	89.3 ppb
Total UFs	30
Intraspecies UF	10
Interspecies UF	1
Subchronic-to-chronic UF	3
Incomplete Database UF Database Quality	1 High
Chronic ReV (HQ = 1)	**3.0 ppb (8.7 µg/m^3)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**0.9 ppb (2.6 µg/m^3)**

4.1.9 Comparison of TCEQ's Chronic ReV to other Long-Term, Health-Protective Comparison Levels from Other Agencies

Table 7 presents a comparison of the TCEQ chronic ReV to long-term, health-protective comparison values developed by other agencies. All the values are considered health protective of the potential chronic effects of chlorine exposure, despite differences in their derivations. For example, all values provide more than an order of magnitude margin of exposure compared to the exposure concentrations in Klonne et al. (1987) associated with trace, non-biologically significant changes (i.e., all values are > 30-fold lower than 0.1 and 0.5 ppm).

Note that all agencies besides the TCEQ developed chronic inhalation toxicity factors before new animal-to-human dosimetric adjustment guidelines were published in 2012 (USEPA 2012). In the case of the chronic MRL, this results in decreasing the POD value 3-fold. When combined with an additional ATSDR UF_A of 3 for TD, the result is a 10-fold decrease in the ATSDR POD for extrapolation from monkeys to humans (in addition to applying an intrahuman UF_H of 10). Like the TCEQ's exposure duration adjustment, ATSDR's duration adjustment equates to another factor of 5.6 (i.e., for division of the POD_{HEC}). However, it seems the most important difference is that ATSDR (2010) used benchmark dose (BMD) modeling to derive a POD based on the 95% lower confidence limit on the concentration for a 10% extra risk of hyperplasia of the nasal epithelium ($BMCL_{10}$ of 20 ppb) without apparent regard to biological significance/adversity when the study authors themselves indicated that at chlorine concentrations ≤ 500 ppb (i.e., concentrations up to 25-fold higher than ATSDR's POD) changes were trace/very minimal (even occurring in one (12.5%) of the control monkeys) and most importantly, of questionable biological significance (i.e., adversity). For example, while extensive areas of deciliation in the nasal passages can impair mucociliary function/clearance in affected regions of the nose, only small/limited areas of impaired ciliary function were observed in this study. Additionally, exposure to ≤ 2.3 ppm did not induce any pulmonary effects (e.g., lesions, edema), much less any indicative of potential impairment of pulmonary defenses. These considerations lend support to 500 ppb as a LOEL consistent with the questionable biological significance characterization of effects at ≤ 0.5 ppm by study authors. In regard to the basis for the 2000 OEHHA chronic REL, the TCEQ agrees with ATSDR (2010) that primates are a better model to evaluate potential respiratory effects in humans than rodents (i.e., rats).

Table 7. Long-Term, Health-Protective Comparison Levels Developed by the TCEQ and Other Agencies

Agency	Long-Term Comparison Value Name	Long-Term Comparison Value	POD_{HEC}	Total UF	Key Study and Critical Effect
TCEQ (2017)	Reference Value (ReV)	3.0 ppb	89.3 ppb $LOEL_{HEC}$	30	Klonne et al. (1987); Ocular irritation and mild focal nasal and tracheal mucosal lesions in Rhesus monkeys
ATSDR (2010)	Minimal Risk Level (MRL)	0.05 ppb	1.36 ppb $BMCL_{10\text{-}HEC}$	30	Klonne et al. (1987); Hyperplasia of nasal epithelium in Rhesus monkeys
OEHHA (2000a)	Reference Exposure Level (REL)	0.08 ppb	2.4 ppb $BMC_{05\text{-}HEC}$	30	Wolf et al. (1995); Upper respiratory epithelial lesions in rodents (i.e., rats)

Lastly, it is noted that the chronic ReV for chlorine (Cl_2) of 8.7 μg/m^3 (3.0 ppb) is within a factor of 3 of (i.e., 2.9-fold lower than) the chronic ReV for HCl on a chlorine content basis (i.e., HCl chronic ReV of 26 μg/m^3 × MW of Cl/MW of HCl = 26 μg/m^3 × 35.45/36.46 = 25 μg/m^3 as Cl; TCEQ 2015c). This is a reasonable difference considering, for example, that the original authors of the different studies selected the exposure concentrations that ultimately determined the study PODs (i.e., NOAELs) in both cases and that the values of UFs used to reduce PODs are generally limited to factors of 3 and 10. Interestingly, despite similar rat endpoints (i.e., upper respiratory tract epithelial lesions), the chronic REL for chlorine of 0.08 ppb is over 70-fold lower than the chronic REL for HCl adjusted for chlorine content (6 ppb × 35.45/36.46 = 5.8 ppb; OEHHA 200b), which would not necessarily be expected based on the MOAs. Similarly, the chronic REL for HCl adjusted for chlorine content (5.8 ppb) is over 100-fold higher than the chronic MRL for chlorine (0.05 ppb). By contrast, the chronic REL for HCl adjusted for chlorine content (5.8 ppb) is within a factor of 2 of the TCEQ chronic ReV for chlorine (3.0 ppb).

4.2 Carcinogenic Potential

There is no definitive evidence that chlorine has carcinogenic potential. For example, no increase in neoplasms was reported in an epidemiology study of chlorine production workers with time-weighted exposures of 6-1,420 ppb (Patil et al. 1970 as cited by NRC 2004). Additonally, no increased incidences of neoplasms ocurred in F344 rats exposed by inhalation up to 2.5 ppm chlorine for 2 years or in F344 rats and B6C3F1 mice exposed via drinking water for 2 years (CIIT 1993, Wolf et al. 1995, and NTP 1992 as cited by NRC 2004).

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term effects of chlorine on vegetation.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV = 3.0 ppb (8.7 µg/m^3)
- $^{chronic}ESL_{threshold(nc)}$ = 0.9 ppb (2.6 µg/m^3)

The chronic ReV of 3.0 ppb (8.7 µg/m^3) will be used for the evaluation of any ambient air monitoring data (Table 1). The $^{chronic}ESL_{threshold(nc)}$ of 0.9 ppb (2.6 µg/m^3) is the long-term ESL used for air permit reviews (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is not used to evaluate any ambient air monitoring data.

Chapter 5 References

Agency for Toxic Substances and Disease Registry (ATSDR). 2010. Toxicological profile for chlorine. US Department of Health and Human Services. Division of Toxicology and Environmental Medicine/Applied Toxicology Branch, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333. Available from: http://www.atsdr.cdc.gov/ToxProfiles/tp172.pdf.

American Chemistry Council. 2010. The economic benefits of chlorine chemistry. Available from: https://chlorine.americanchemistry.com/ContentConversion/Chlorine-Chemistry-to-Your-State/TX.pdf.

American Chemistry Council webpage on Chlorine Production. Available from: https://chlorine.americanchemistry.com/Chlorine/ChlorineProduction/.

American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices – Chlorine. Cincinnati, OH.

American Industrial Hygiene Association (AIHA). 1988. Emergency Response Planning Guidelines, Chlorine. Akron, OH: AIHA.

American Industrial Hygiene Association (AIHA). 1989. Odor Thresholds for Chemicals with Established Occupational Health Standards. Akron, Ohio.

Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3:272-290.

Anglen DM. Sensory response of human subjects to chlorine in air [PhD dissertation]. Ann Arbor (MI): University Microfilms International; 1981.

Arts JH, C de Heer, and RA Woutersen. 2006. Local effects in the respiratory tract: relevance 1 of subjectively measured irritation for setting occupational exposure limits. Int Arch 2 Occup Environ Health 79:283-298.

Barrow CS, Kociba RJ, Rampy LW, et al. 1979. An inhalation toxicity study of chlorine in Fisher-344 rats following 30 days of exposure. Toxicol Appl Pharmacol 49:77-88.

Baxter PJ, Davies PC, Murray V. Medical planning for toxic releases into the community: the example of chlorine gas. Br J Ind Med 1989; 46:277-285.

Benedict HM and Breen WH. 1955. The use of weeds as a means of evaluating vegetation damage caused by air pollution. Proc Third Nat Air Pollution Symposium, p. 177. Pasadena, California.

Bherer L, Cushman R, Courteau JP, Quevillon M, Cote G, Bourbeau J, L'Archeveque J, Cartier A, and Malo JL. 1994. Survey of construction workers repeatedly exposed to chlorine over a three to six month period in a pulpmill: II. Follow up of affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24 months after exposure ended. Occup Environ Med 51:225-228.

Brennan E, Leone I, Daines RH. 1965. Chlorine as a phytotoxic air pollutant. International Journal of Air and Water Pollution 9:791-797.

Budavari, S, O'Neil MJ, Smith A, Heckelman PE, and Kinneary JF, eds. 1996. The Merck Index, 12th Ed. Rahway, NJ: Merck & Co., Inc.

Chang-Yeung M, Lam S, Kennedy SM, and Frew AJ. 1994. Persistent asthma after repeated exposure to high concentrations of gasses in pulpmills. Am J Respir Crit Care Med 149:1676-1680.

Chester EH, Gillespie DG, and Krause FD. 1969. The prevalence of chronic obstructive pulmonary disease in chlorine gas workers. Am Rev Respir Dis 99(3):365-373.

Chemical Industry Institute of Toxicology (CIIT). 1993. A chronic inhalation toxicity study of chlorine in female and male B6C3F$_1$ mice and Fischer 344 rats. Research Triangle Park, NC: CIIT.

Courteau JP, Cushman R, Bouchard F, Quevillon M, Chartrand A, and Bherer L. 1994. Survey of construction workers repeatedly exposed to chlorine over a three to six month period in a pulpmill: I. Exposure and symptomatology. Occup Environ Med 51(4):219-224.

D'Alessandro A, Kuschner W, Wong H, Boushey HA, Blanc PD. 1996. Exaggerated responses to chlorine inhalation among persons with nonspecific airway hyperreactivity. Chest 109(2):331-337.

Dixon GA and Ikels KG. 1977. Olfactory threshold of chlorine in oxygen. National Technical Information Service Department of Commerce. 5285 Port Royal Rd, Springfield, VA 22161. Code A.

Donnelly SC, and Fitzgerald MX. 1990. Reactive airways dysfunction syndrome (RADS) due to chlorine gas exposure. Ir J Med Sci 159:275-277.

Enarson D, Johnson A, Block G, Schragg K, Maclean L, Dybuncio A, Chan-Yeung M, and Grzybowski S. 1984. Respiratory health at a pulpmill in British Columbia Arch Environ Health 39:325-330.

Ferris BG, Burgess WA, Worcester J. 1967. Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Br J Ind Med 24:26-37.

Ferris BG, Puleo S, Chen HY. 1979. Mortality and morbidity in a pulp and a paper mill in the United States: A ten-year follow-up. Br J Ind Med 36:127-134.

Gautrin D, Boulet LP, Boutet M, Dugas M, Bherer L, L'Archeveque J, Laviolette M, Cote J, and Malo JL. 1994. Is reactive airways dysfunction syndrome a variant of occupational asthma? J Allergy Clin Immunol 93:12-22.

Griffiths RF and Smith LE. 1990. Development of a vegetation-damage indicator as a means of post-accident investigation for chlorine releases. Journal of Hazardous Materials 23: 137-165.

Harkema J, Carey S, and Wagner J. 2006. The nose revisited: a brief review of the comparative structure, function, and toxicologic pathology of the nasal epithelium. Toxicol Pathol 34:252-269.

Hazardous Substances Database (HSB). 2010. National Institutes of Health, National Library of Medicine, Bethesda, Maryland. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Ibanes JD, LeinigerJR, Jarabek AM, et al. 1996. Reexamination of respiratory tract response in rats, mice and rhesus monkeys chronically exposed to inhaled chlorine. Inhal Toxicol 8:859-876.

Joosting P and Verberk M. 1974. Emergency population exposure: A methodological approach. Recent Adv Assess Health Eff Environ Pollut 4:2005-2029.

Kennedy SM, Enarson DA, Janssen RG, and Chan-Yeung M. 1991. Lung health consequences of reported accidental chlorine gas exposures among pulpmill workers. Am Rev Respir Dis 143:74-79.

Klonne D, Ulrich C, Riley M, Hamm T, Morgan K, and Barrow C. 1987. One-year inhalation toxicology study of chlorine in Rhesus monkeys (Macaca mullata). Fundam Appl Toxicol 9:557-572.

Kutzman RS. 1983. A study of Fisher-344 rats subchronically exposed to 0, 0.5, 1.5, or 5.0 ppm chlorine. Upton, NY: Brookhaven National Laboratory. BNL 32710.

Leonardos, G.; Kendall, D.; Barnard, N. (1969). Odor Threshold Determination of 53 Odorant Chemicals. J. Air Pollut. Control Assoc. 19:91-95.

Nagata Y. 2003. Measurement of odor threshold by triangle odor bag method. Odor Measurement Review, Japan Ministry of the Environment.

National Institute for Occupational Safety and Health (NIOSH). 1976. Criteria for a recommended standard: Occupational exposure to chlorine. NIOSH Publication 76-170. US Department of Health and Human Services, Washington, DC.

National Research Council (NRC). 2004. Chlorine: acute exposure guideline levels. Acute exposure guideline levels for selected airborne chemicals. Vol.4. pp 13-76. The National Academies Press, Washington, DC. Available from: https://www.epa.gov/sites/production/files/2014-11/documents/tsd56.pdf.

National Toxicology Program (NTP). 1992. Toxicology and carcinogenesis studies of chlorinated water (CAS Nos. 7782-50-5 and 7681-52-9) and chloraminated water (CAS No. 10599-90-3) (deionized and charcoal-filtered) in F344/N rats and B6C3F1 mice (drinking water studies). Research Triangle Park, NC: National Toxicology Program. NTP TR-392. NIH Publication No. 92-2847.

Office of Environmental Health Hazard Assessment (OEHHA). 1999. Acute Toxicity Summary. Chlorine. Determination of acute reference exposure levels. Appendix D2 pp 53-61. California Environmental Protection Agency, Berkeley, CA. Available from: http://www.oehha.ca.gov/air/hot_spots/2008/AppendixD2_final.pdf#page=32.

Office of Environmental Health Hazard Assessment (OEHHA). 2000a. Chronic Toxicity Summary. Chlorine. Determination of noncancer chronic reference exposure levels. Appendix D3 pp 106-113. California Environmental Protection Agency, Berkeley, CA. Available from: http://www.oehha.ca.gov/air/hot_spots/2008/AppendixD3_final.pdf#page=66.

Office of Environmental Health Hazard Assessment (OEHHA). 2000b. Chronic Toxicity Summary. Hydrogen Chloride. Determination of noncancer chronic reference exposure levels. Appendix D3 pp 309-312. California Environmental Protection Agency, Berkeley, CA. Available from: http://www.oehha.ca.gov/air/hot_spots/2008/AppendixD3_final.pdf#page=66.

Patil L, Smith R, Vonwald A, and Mooney T. 1970. The health of diaphragm cell workers exposed to chlorine. Am Ind Hyg Assoc J 31:678-686.

Phillips K, Bales K, Capitanio J, et al. 2014. Why primate models matter. Am J Primatol 76: 801–827.

Rea W, Ross G, Johnson A, Smiley R, Sprague D, Fenyves E, and Samandi N. 1989. Confirmation of chemical sensitivity by means of double-blind inhalant challenge of toxic volatile chemicals. Clin Ecol. 6:113-118.

Rotman HH, Fliegelman MJ, Moore T, et al. 1983. Effects of low concentrations of chlorine on pulmonary function in humans. J Appl Physiol 54(4):1120-1124.

Schins RP, Emmen H, Hoogendijk L, et al. 2000. Nasal inflammatory and respiratory parameters in human volunteers during and after repeated exposure to chlorine. (Comment in: Eur Respir J 19(2):381-382). Eur Respir J 16(4):626-632.

Schreuder MDJ and Brewer CA. 2001. Effects of short-term, high exposure to chlorine gas on morphology and physiology of *Pinus ponderosa* and *Pseudotuga menzieii*. Annals of Botany 88: 187-195.

Shusterman D, Murphy MA, Balmes J. 1998. Subjects with seasonal allergic rhinitis and nonrhinitic subjects react differentially to nasal provocation with chlorine gas. J Allergy Clin Immunol 101(6 Pt 1):732-740.

Shi Z. 1990. Effects of long-term exposure to low concentration of chlorine on workers' health. In: Sakurai H; Okazaki I; Omae K, eds. Occupational Epidemiology, Proceedings of the seventh international symposium on epidemiology in occupational health. Tokyo, Japan. 1989. Pp. 173-177.

ten Berge WF, Zwart A, Appelman LM. 1986. Concentration-time mortality response relationship of irritant and systemic acting vapours and gases. J Hazard Materials 13: 301-309.

Thornton NC, Setterstrom C. 1940. Toxicity of ammonia, chlorine, hydrogen cyanide, hydrogen sulphide, and sulphur dioxide gases. III. Green plants. Boyce Thompson Institute for Plant Research 11: 343-356.

Texas Commission on Environmental Quality (TCEQ). 2015a. TCEQ Guidelines to Develop Toxicity Factors. Available from http://www.tceq.texas.gov/publications/rg/rg-442.html.

Texas Commission on Environmental Quality (TCEQ). 2015b. Approaches to Derive Odor-Based Values. Available from http://www.tceq.texas.gov/toxicology/esl/guidelines/about.html/#pp].

Texas Commission on Environmental Quality (TCEQ). 2015c. Development Support Document for Hydrogen Chloride. Available from: https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/final/sept15/hydrogen_chloride.pdf.

United States Environmental Protection Agency (USEPA). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. (EPA/600/8-90/066F). Washington, D.C.

United States Environmental Protection Agency (USEPA). 1996. Chlorine. Integrated Risk Information System (IRIS). Available from: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=405.

United States Environmental Protection Agency (USEPA). 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment (EPA/600/R-12/044) Washington, DC.

Withers RMJ and Lees FP. 1985. The assessment of major hazards: the lethal toxicity of chlorine. Part 1. Review of information on toxicity. J Hazard Mater 12:231-282

Wolf DC, Morgan KT, Gross EA, Barrow C, Moss OR, James RA, and Popp JA. 1995. Two-year inhalation exposure of female and male B6C3F1 mice and F344 rats to chlorine gas induces lesions confined to the nose. Fundam Appl Toxicol 24:111-131.

World Health Organization (WHO). 1982. Chlorine and hydrogen chloride. Environmental Health Criteria 21. Geneva, Switzerland: World Health Organization.

Zimmerman PW. 1955. Chemicals involved in air pollution and their effects upon vegetation. Contr Boyce Thompson Inst. PI. Res. 3, 124.