Development Support Document
Final, March 14, 2014
Revised Odor Value: September 14, 2015

n-Butyraldehyde

CAS Registry Number:

123-72-8

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TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Revision History

Original Development Support Document (DSD) posted as final on March 14, 2014.

Revised DSD September 14, 2015: the odor-based value was updated based on n-butyraldehyde having a pleasing odor at low concentrations but an offensive odor at higher concentrations (TCEQ 2015).

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
AIHA	American Industrial Hygiene Association
AMCV	air monitoring comparison value
$^{\circ}C$	degrees Celsius
DSD	development support document
ESL	effects screening level
$^{acute}ESL$	acute health-based effects screening level for chemicals meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based effects screening level
$^{acute}ESL_{veg}$	acute vegetation-based effects screening level
$^{chronic}ESL_{threshold(nc)}$	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
$^{chronic}ESL_{veg}$	chronic vegetation-based effects screening level
h	hour
Hg	mercury
HEC	human equivalent concentration
HPV	high production volume
HQ	hazard quotient
IARC	International Agency for Research on Cancer
kg	kilogram
LOAEL	lowest-observed-adverse-effect-level
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

Acronyms and Abbreviations	Definition
min	minute
MOA	mode of action
n	number
NOAEL	no-observed-adverse-effect-level
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
ReV	reference value
RGDR	regional gas dose ratio
TCEQ	Texas Commission on Environmental Quality
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

Chapter 1 Summary Tables and Figure

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values from an acute and chronic evaluation of n-butyraldehyde. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2012) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs) and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on n-butyraldehyde's physical/chemical data.

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

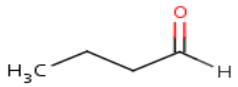
Short-Term Values	**Concentration**	**Notes**
Acute ReV [1h] (HQ = 1.0)	11,000 µg/m^3 (3,800 ppb) **Short-Term Health**	**Critical Effect(s):** Free-standing NOAEL due to lack of irritation or general systemic effects observed in human volunteers
$^{acute}ESL_{odor}$	27 µg/m^3 (9.2 ppb) **Odor**	50% odor recognition population thresholds Characteristic, pungent odor at high concentration; cocoa musty green malty bready odor at low concentration
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	100 µg/m^3 (34 ppb) **Long-Term Health**	**Critical Effect(s):** Hyperplasia, inflammation, and squamous metaplasia of the nasal tissues in rats and dogs
$^{chronic}ESL_{nonthreshold\ (c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
$^{chronic}ESL_{veg}$	---	No data found

Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	**Concentration**	**Notes**
^{acute}ESL [1 h] (HQ = 0.3)	3,300 µg/m^3 (1,100 ppb) [a]	**Critical Effect(s)**: Free-standing NOAEL due to lack of irritation general systemic effects observed in human volunteers
^{acute}ESL$_{odor}$	27 µg/m^3 (9.2 ppb) **Short-term ESL for Air Permit Reviews**	50% odor recognition population thresholds Characteristic, pungent odor at high concentration; cocoa musty green malty bready odor at low concentration
^{acute}ESL$_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
^{chronic}ESL$_{threshold(nc)}$ (HQ = 0.3)	30 µg/m^3 (10 ppb) [b] **Long-term ESL for Air Permit Reviews**	**Critical Effect(s)**: Hyperplasia, inflammation, and squamous metaplasia of the nasal tissues in rats and dogs
^{chronic}ESL$_{nonthreshold(c)}$	---	Data are inadequate for an assessment of human carcinogenic potential
^{chronic}ESL$_{veg}$	---	No data found

[a] Based on the acute ReV of 11,000 µg/m^3 (3,800 ppb) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.
[b] Based on the noncarcinogenic chronic ReV of 100 µg/m^3 (34 ppb) multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	C_4H_8O	ChemIDplus 2012
Chemical Structure		ChemIDplus 2012
Molecular Mass	72.1 g/mole	AIHA 2004
Physical State	Liquid	AIHA 2004
Color	Colorless	AIHA 2004
Odor	Characteristic pungent, aldehyde odor	AIHA 2004
CAS Registry Number	123-72-8	AIHA 2004
Synonyms	Butal; butaldehyde; butalyde; butanal; butanaldehyde; butyric aldehyde; butyl aldehyde; butyral	AIHA 2004
Solubility in water	7,100 mg/L @ 25°C	AIHA 2004
Log K_{ow}	0.88	ChemIDplus 2012
Vapor Pressure	111 mm Hg @ 25°C	ChemIDplus 2012
Vapor Density (air = 1)	2.5	AIHA 2004
Density/Specific Gravity (water = 1)	0.80 @ 20°C	AIHA 2004
Melting Point	-80°C	AIHA 2004
Boiling Point	74.8°C @ 760 mm Hg	AIHA 2004
Conversion Factors	1 ppm = 2.95 mg/m^3 @ 25°C 1 mg/m^3 = 0.34 ppm	AIHA 2004

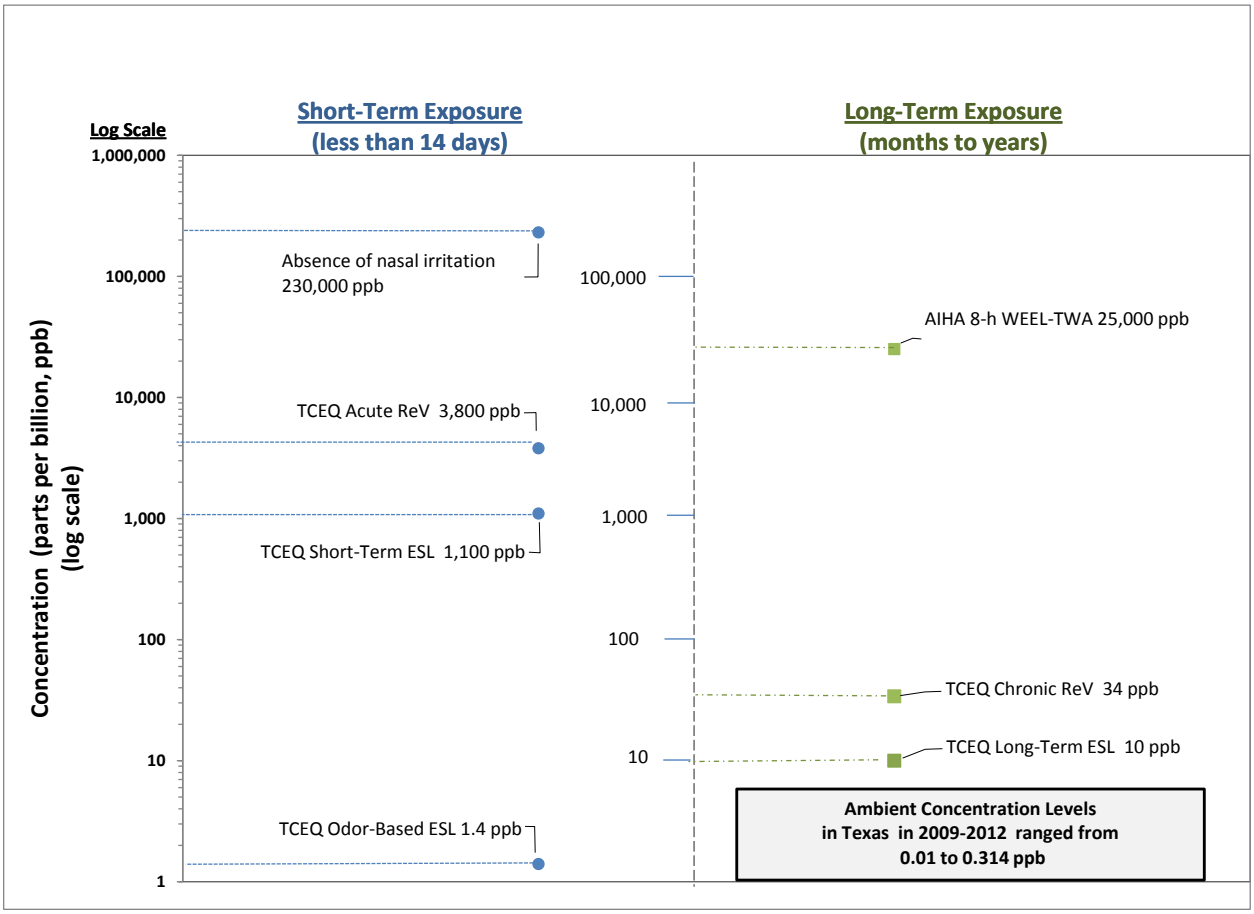


Figure 1. n-Butyraldehyde Health Effects and Regulatory Levels

Figure 1 compares n-butyraldehyde acute toxicity values (acute ReV, $^{acute}ESL_{odor}$, and health-based $^{acute}ESL$) and chronic toxicity values (chronic ReV and long-term ESL) found in Tables 1 and 2 to the air concentrations associated with nasal irritation, and the time-weighted average (TWA) workplace environmental exposure level (WEEL) set by the American Industrial Hygiene Association (AIHA).

Chapter 2 Major Sources or Uses and Ambient Air Concentrations

2.1 Major Sources or Uses

n-Butyraldehyde is listed as a High Production Volume (HPV) chemical. Chemicals listed as an HPV chemical were produced in or imported into the U.S. in quantities greater than one million pounds in 1990 and/or 1994 (USEPA 2009, as cited in HSDB 2012). According to the United States Environmental Protection Agency (USEPA), "n-butyraldehyde is used as an intermediate in the production of synthetic resins, rubber accelerators, solvents, plasticizers, and high molecular weight polymers" (USEPA 1994). According to the American Industrial Hygiene Association (AIHA), "n-butyraldehyde is also used as a synthetic flavoring agent in foods such

as alcoholic and non-alcoholic beverages, ice cream, candy and baked goods." It is considered "generally recognized as safe" as a food additive by the U.S. Food and Drug Administration (AIHA 2004). n-Butyraldehyde is also one of the aldehyde components of main stream cigarette smoke (Hoberman et al. 1988). The amount of n-butyraldehyde in main stream cigarette smoke ranges from 88.6-928.3 μg/cigarette (van Andel et al. 2006)

2.2 Background Levels of n-Butyraldehyde in Ambient Air

Measurable levels of atmospheric n-butyraldehyde are associated with industrial sources. The gas-phase concentration of n-butyraldehyde in ambient Los Angeles air during photochemical pollution episodes (July-Oct 1980) ranged from 0 to 7 ppb with a median concentration of about 1.5 ppb. A field monitoring study along a highway in Raleigh, North Carolina USA in May 1983 detected n-butyraldehyde levels of 2.88-7.29 ppb (HSDB 2012). According to the USEPA's fact sheet, the half-life of n-butyraldehyde in air is 16.4 hours. Its removal from air occurs primarily through reaction with photochemically-produced hydroxyl radicals (USEPA 1994). In Texas, ambient 24-h network data (carbonyl samples) showed that measured levels of n-butyraldehyde ranged from 0.01 to 0.314 ppb in Houston, El Paso, Tyler, and Dallas from 2009-2012. The highest 24-hour sample of 0.314 ppb occurred in El Paso.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

n-Butyraldehyde is of low acute toxicity by oral, dermal, or inhalation routes of exposure. Acute exposure to high ambient concentration can cause irritation of the eyes, nose, and throat with narcosis or anesthesia (AIHA 2004).

3.1.1 Physical/Chemical Properties

n-Butyraldehyde is a highly flammable, colorless liquid with a characteristic pungent odor (AIHA 2004). n-Butyraldehyde is soluble in water. It has a relative high vapor pressure and is present as vapor in air. The main chemical and physical properties of n-butyraldehyde are summarized in Table 3.

3.1.2 Key and Supporting Studies

Information regarding the acute toxicity of n-butyraldehyde in humans is limited to one study (Sim and Pattle 1957). The Sim and Pattle (1957) human study was selected as the key study to develop the acute ReV. As human data are preferred for ReV development (TCEQ 2012), other animal acute and subacute studies were used as supporting studies.

3.1.2.1 Key Human Study (Sim and Pattle 1957)

In a controlled inhalation study by Sim and Pattle (1957), a group of 15 healthy men aged 18 to 45 years, were exposed to 230 ppm (690 mg/m^3, measured concentration) n-butyraldehyde for 30 minutes (min). All the subjects were exposed simultaneously in a 100-m^3 exposure chamber.

Unexposed men were used as controls. Blood pressure, pulse rates, and respiratory rates were recorded before, during, and after each exposure. Electrocardiograms were also recorded for a certain number in each group before and after exposure. No mucous membrane irritation to eye, nose, or the upper respiratory tract was observed in all exposed men. A free-standing no-observed-adverse-effect-level (NOAEL) of 230 ppm for irritation was identified from this study. The NOAEL was used as a point of departure (POD) to develop the acute ReV.

3.1.2.2 Supporting Animal Studies

3.1.2.2.1 Steinhagen and Barrow (1984) Study

Steinhagen and Barrow (1984) performed a sensory irritation study in B6C3F1 and Swiss-Webster mice. Mice were exposed to various concentrations of one of several aldehyde vapors for 10 min in a head-only exposure chamber. Sensory irritation was quantified by measuring respiratory rate depression during exposure, and five concentrations of each aldehyde were used to determine the concentration resulting in a 50% decrease in respiratory rate (RD_{50}). The RD_{50} values for n-butyraldehyde calculated by the authors were 1,532 ppm and 1,015 ppm for B6C3F1 and Swiss-Webster mice, respectively.

3.1.2.2.2 USEPA (1989a) Acute Study

An acute inhalation study was performed by Bio/Dynamics, Incorporated on behalf of Hoechst Celanese Corporation in 1981 and submitted to USEPA (USEPA 1989a). Five male and five female Sprague-Dawley (SD) rats were exposed to n-butyraldehyde vapor for 4 hours (h) at a target chamber concentration of 2,200 ppm (the actual mean chamber concentration was 1,820 ppm). Rats were observed during the exposure and for 14 days (d) after exposure. Within 15 min of exposure, most rats had partially closed their eyes. Chromodacryorrhea (bloody tears) was observed in some rats within 30 min of exposure, and a red nasal discharge was observed in some rats after 180 min. Following exposure, all rats exhibited lacrimation (weeping eyes) and conjunctiva swelling. These symptoms were alleviated within 4 h post-exposure. Small, transient weight loss was seen in both sexes following exposure. Body weights recovered to pre-exposure values by post-exposure day 2 in most males and by post-exposure day 7 in most females. A free-standing lowest-observed-adverse-effect-level (LOAEL) of 1,820 ppm was identified from this study. Because only one dose was tested, which produced notable point of entry (POE) effects some of which were severe; the TCEQ does not consider this study to be appropriate for the development of an acute toxicity factor.

3.1.2.2.3 USEPA (1992a) Nine-Day Study

A subacute inhalation study was performed by Carnegie-Mellon on behalf of DuPont Chemical in 1978 and submitted to the USEPA (USEPA 1992). Groups of five SD rats, five Fischer 344 rats, five albino mice, three albino Guinea pigs, one rabbit, and one dog were exposed to n-butyraldehyde vapor for 6 h/d, 5 d/week for 9 d over a 2-week period at target chamber concentrations of 0, 2,000, 4,000, and 8,000 ppm (analytical average chamber concentrations were 0.05, 2,000, 3,100, and 6,400 ppm). Exposure to 6,400 ppm resulted in the death of the

majority of tested animals within 9 d. The principle cause of death was determined to be respiratory failure. Indications of corneal damage, including dullness and 5-10% necrosis, were observed in rabbits at 3,100 ppm. No signs of corneal injury were observed at 2,000 ppm. Decreased body weight was observed in all animals exposed to 6,400 and 3,100 ppm. The only statistically significant weight loss observed at 2,000 ppm occurred in the Fischer rats, which had developed pneumonia that was not likely associated with exposure to n-butyraldehyde, since it occurred at a similar rate in control animals. Statistically significant differences in mean liver weight values compared to the mean control values were found for the SD (both sexes) and male Fischer rats at 3,100 ppm. Definite signs of eye and respiratory irritation, and statistically significant lower body weight findings were observed in most species inhaling 6,400 and 3,100 ppm of n-butyraldehyde. Only slight eye and respiratory irritation, including lacrimation, conjunctivitis, salivation, nasal discharge, and audible respiration, were observed in all animals at 2,000 ppm. A free-standing LOAEL of 2,000 ppm for body weight loss and mild sensory irritation was identified from this study.

3.1.2.2.4 Gage (1970) Study

In a review of subacute inhalation toxicity for 109 industrial chemicals by Gage (1970), three male and four female Alderley Park specific-pathogen-free rats with an average weight of 200 g were exposed to 1,000 ppm n-butyraldehyde vapor concentration 6 h/d for 12 d. No sensory irritation or other clinical effects were observed. Histological evaluation of the lung did not find any toxic response. The level of 1,000 ppm is considered a free-standing NOAEL.

3.1.2.2.5 USEPA (1989b) Subacute Study

An additional subacute inhalation study was performed by Bio/Dynamics Incorporated on behalf of Monsanto in 1979 and submitted to the USEPA (USEPA 1989b). One hundred SD rats (40 control animals and 20 animals per dose group) equally divided by sex were exposed to n-butyraldehyde vapor for 6 h/d, 5 d/week for 4 weeks at target chamber concentrations of 0, 300, 900, and 3,000 mg/m^3. Actual mean chamber concentrations were 293, 930, and 2710 mg/m^3, which correspond to 100, 316, and 921 ppm. Study endpoints included body weights, urinalysis, blood chemistry, hematology, and pathology. All animals survived for the duration of the study. Mean body weights did not differ between controls and all exposure groups. Male rats exposed to the highest dose of n-butyraldehyde displayed slightly depressed red blood cell counts, and slightly elevated hemoglobin values were detected in female rats exposed to the highest dose. These hematological endpoints were not considered toxicologically significant. Clinical chemistry results were within normal biological limits for all endpoints evaluated. There was a statistically significant increase in the mean adrenal/body weight ratio for male rats in the highest exposure group compared to controls. There was also a statistically significant increase in the mean lung/body weight ratio for both male and female rats in the highest exposure group compared to controls. A dose-response relationship was observed in lung/body weight ratio. The pathology report did not identify any treatment-related gross or microscopic changes in any of the exposure groups. A NOAEL of 316 ppm (930 mg/m^3) was identified from this study.

Table 4 is a summary of acute exposure data from key and supporting studies, arranged from short duration to longer duration studies.

Table 4. Acute n-Butyraldehyde Inhalation Toxicity

Exposure Concentrations (Species)	Exposure Time	NOAEL	LOAEL	End Point (Reference)
230 ppm (15 healthy men)	30 min	230 ppm (Free-standing)		Absence of irritation. (Sim and Pattle 1957, Key Study)
unknown (B6C3F1 mice)	10 min	RD_{50} = 1,015 ppm		50% decrease in respiratory rate (Steinhagen and Barrow 1984)
unknown (Swiss-Webster mice)	10 min	RD_{50} = 1,532 ppm		50% decrease in respiratory rate (Steinhagen and Barrow 1984)
1,820 ppm (SD rats)	4 h		1,820 ppm (Free-standing)	Lacrimation and conjunctiva swelling, transient weight loss (USEPA 1989a)
0.05, 2,000, 3,100, and 6,400 ppm (SD and Fischer 344 rats)	6 h/d, 5 d/week for 9 d		2,000 ppm (Free-standing)	Body weight loss and mild sensory irritation (USEPA 1992a)
1,000 ppm (Alderley Park rats)	6 h/d for 12 d	1,000 ppm (Free-standing)		Absence of sensory irritation or other clinical effects (Gage 1970)
0, 100, 316, and 921 ppm (SD rats)	6 h/d, 5 d/week for 4 weeks	316 ppm	921 ppm	Increase in the mean lung/body weight ratio (USEPA 1989b)

3.1.3 Reproductive/Developmental Toxicity Studies

The potential reproductive and developmental inhalation toxicities of n-butyraldehyde have not been studied in humans or animals. n-Butyraldehyde is expected to be rapidly oxidized to butyric acid by aldehyde dehydrogenase and would not be expected to accumulate in humans. Following inhalation, aliphatic aldehydes (e.g., n-butyraldehyde) are known to induce mainly local effects at the site of exposure and a few systemic effects (e.g., localized lesions) probably due to little absorption through the respiratory tract (van Andel et al. 2006). There would be insignificant

distribution remote to the respiratory tract, so reproductive/developmental effects would be minimized at low concentrations that protect against mild sensory and respiratory effects in humans.

3.1.4 Mode of Action (MOA) Analysis

The MOA of n-butyraldehyde for sensory irritation, which appears to be the critical effect, is unknown. However, the responses may be associated with the crosslinking of aldehydes with proteins (Steinhagen and Barrow 1984). Because the hydrated form of an aldehyde may be responsible for protein crosslinking, the relative potency of an aldehyde may be related to the degree to which it hydrates. In addition, the MOA is similar to that for formaldehyde (TCEQ 2008) and thus, the MOA for minor eye or sensory irritation after exposure to n-butyraldehyde may involve interaction with local nerve endings or trigeminal stimulation.

3.1.5 Dose Metric

Since the key study is based on human volunteers exposed to the parent chemical, exposure concentration of the parent chemical will be used as the default dose metric.

3.1.6 POD for the Key Study and Critical Effect

The 30-min free-standing NOAEL of 230 ppm for absence of sensory irritation observed in the Sim and Pattle (1957) human inhalation study was used as the POD to derive the acute ReV for n-butyraldehyde. Eye and respiratory irritation was observed in several acute and subacute animal studies. The sensory irritation observed in animals is assumed similar to humans. Additionally, irritation of mucous surfaces was reported in healthy men exposed to other aldehydes, i.e., formaldehyde, acetaldehyde, and crotonaldehyde (Sim and Pattle 1957). Thus, upper respiratory tract irritation is considered the critical effect for acute n-butyraldehyde exposures.

3.1.7 Dosimetric Adjustments

3.1.7.1 Exposure Duration Adjustments

The POD from the Sim and Pattle (1957) human inhalation study is based on a free-standing NOAEL of 230 ppm for irritation. Since eye or respiratory irritation is a concentration-dependent effect, a duration adjustment from 30-min to 1 h was not applied. Therefore, the 30-min POD_{HEC} applicable for a 1-h exposure is 230 ppm.

3.1.7.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Since the POD_{ADJ} is based on human volunteer exposure, the POD_{ADJ} of 230 ppm was directly used as a human equivalent concentration (POD_{HEC}) to set the acute ReV.

3.1.8 Adjustments of the POD_{HEC}

The MOA by which n-butyraldehyde produces irritation is assumed to have a threshold for the response, so a POD was determined and uncertainty factors (UFs) were applied to derive an acute ReV. The following UFs were applied to the POD_{HEC} of 230 ppm:

- a full UF_H of 10 was used to account for intraspecies variability;
- a UF_D of 6 was used because the acute database for n-butyraldehyde includes only one acute inhalation study in humans (key study); one acute and three subacute animal inhalation exposure supporting studies in multiple species. Among these studies, only one study (USEPA 1989b) showed a dose-response relationship in body/organ weight loss. There are no reproductive/developmental toxicity studies although significant systemic absorption is not expected. The quality of the database and key study are considered medium; and the confidence in the acute database is medium; and thus
- the total UF = 60.

Acute ReV = POD_{HEC} / (UF_H x UF_D)
= 230 ppm / (10 x 6)
= 3.833ppm
= 3,800 ppb (11,000 µg/m^3)

3.1.9 Adjustments of POD_{HEC} to Acute ReV and ^{acute}ESL

In deriving the acute ReV, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The rounded ReV of 3,800 ppb (11,000 µg/m^3 was then used to calculate the ESL. The ^{acute}ESL of 1,100 ppb (3,300 µg/m^3) is based on the acute ReV multiplied by a hazard quotient (HQ) of 0.3, then rounded to two significant figures at the end of all calculations (Table 5).

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

Parameter	Summary
Study	Sim and Pattle (1957)
Study Population	Fifteen male volunteers (aged 18-45)
Study Quality	Medium
Exposure Method	Inhalation of 230 ppm (measured concentration) exposure
Exposure Duration	30 min
Critical Effects	Absence of sensory irritation in human volunteers
NOAEL	230 ppm (Free-standing NOAEL)
POD	230 ppm
Extrapolation to 1 h (POD_{ADJ})	230 ppm (no adjustment – effects were concentration dependent)
POD_{HEC}	230 ppm
Total uncertainty factors (UFs)	60
Interspecies UF	N/A
Intraspecies UF	10
LOAEL-to-NOAEL UF	N/A
Incomplete Database UF *Database Quality*	6 Medium
Acute ReV [1 h] (HQ = 1)	**11,000 µg/m^3 (3,800 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**3,300 µg/m^3 (1,100 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

n-Butraldehyde naturally occurs in a variety of food, wines, and fruits. It is widely used as flavorings and perfuming agent. n-Butraldehyde has a characteristic pungent odor at high concentration but has apple, creamy chocolate, ethereal, fruity, vegetative, or bready odor at low concentration. n-Butraldehyde has broad range of odor threshold values. An odor detection threshold of 4.6, 3.1, and 0.67 ppb were reported by Hellman et al. (1973, 1974), van Doorn (2002), and Nagata (2003), respectively. In addition, a 50% and a 100% odor recognition

threshold values of 9.2 and 39 ppb, respectively, were reported by Hellman et al. (1973, 1974). According to the TCEQ Odor Position Paper (TCEQ 2015), if available data indicates the chemical of interest actually has a pleasing odor at low concentrations but an offensive odor at higher concentrations, a higher odor threshold value may be used for the odor-based ESL. Accordingly, the $^{acute}ESL_{odor}$ for n-butyraldehyde is developed at a higher odor threshold value, i.e., a 50% odor recognition threshold value of 9.2 ppb (27 µg/m^3). Because odor is a concentration-dependent effect, the same 1-h $^{acute}ESL_{odor}$ can be assigned to all averaging times for monitoring and modeling samples.

3.2.2 Vegetation Effects

After careful review of the current literature, no information regarding the vegetative toxicity of n-butyraldehyde was found.

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

The acute evaluation resulted in the derivation of the following values for n-butyraldehyde:

- Acute ReV = 11,000 µg/m^3 (3,800 ppb)
- $^{acute}ESL$ = 3,300 µg/m^3 (1,100 ppb)
- $^{acute}ESL_{odor}$ = 27 µg/m^3 (9.2 ppb)

For the evaluation of ambient air monitoring data, both the acute ReV of 11,000 µg/m^3 (3,800 ppb) and $^{acute}ESL_{odor}$ of 27 µg/m^3 (9.2 ppb) are used (Table 1).The short-term ESL for air permit reviews is the $^{acute}ESL_{odor}$ of 27 µg/m^3 (9.2 ppb) as it is lower than the health-based $^{acute}ESL$ of 3,300 µg/m^3 (1,100 ppb) (Table 2).

3.4 Acute Observed Adverse Effect Level

The acute POD from the key study is a free-standing acute NOAEL of 230 ppm in human volunteers. The lowest acute LOAEL is 1,820 ppm for lacrimation and conjunctiva swelling, transient weight loss in rats (USEPA 1989a). However, only one dose (1,820 ppm) was conducted in this study and the free-standing LOAEL is much higher than the NOAEL of 230 ppm in humans. Thus, the acute observed adverse effect level was not calculated.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

No animal studies or reports of adverse human effects from chronic exposure to n-butyraldehyde were found. The effect of most probable concern from chronic low level exposure is respiratory tract irritation as evidenced by increased lung weights in the subacute as well as subchronic inhalation studies (USEPA 1988, 1989a,b). Subchronic inhalation studies in laboratory animals

have demonstrated mortality and localized lesions in response to irritation as well as some effects on hematology and clinical chemistry (USEPA 1994).

4.1.1 Physical/Chemical Properties

For physical/chemical properties, refer to Section 3.1 and Table 3.

4.1.2 Key and Supporting Studies

A series of studies on the subchronic inhalation toxicity of n-butyraldehyde conducted by Union Carbide Corporation in 1979 (unpublished) and submitted to the USEPA in 1988 (USEPA 1988) was selected as the key study for the derivation of chronic toxicity factors. No other subchronic studies were available for supporting studies.

4.1.2.1 Key Animal Study (USEPA 1988)

4.1.2.1.1 Study I

In the Union Carbide Corporation 1979 studies (USEPA 1988), groups of male and female SD rats (20 rats/sex/group) and four male beagle dogs per group were exposed to n-butyraldehyde vapor at target concentrations of 0, 125, 500, or 2,000 ppm (mean measured concentrations of 0, 117, 482, or 1852 ppm) for 6 h/d, 5 d/week, for 13 and 14 weeks, respectively. There was a full investigation with respect to body and organ weights, urinalysis, blood chemistry, pathology and hematological examinations. Clinical signs of ocular and upper respiratory tract irritation occurred at all exposure groups. Histopathologic changes in rats displayed a significant increase in the incidence of squamous metaplasia of the nasal cavity in all treatment groups. The incidence and severity generally decreased with decreasing exposure concentration. Dogs exposed to 117 and 482 ppm displayed goblet cell hyperplasia within the nasal mucosa; dogs in the 1852 ppm treatment group displayed hyperplasia, inflammation, and squamous metaplasia of the nasal tissues. The changes are indicative of a response to repeated upper respiratory tract irritation. No other treatment-related effects (i.e., systemic effects) on body weight, serum chemistry, hematology, urinalysis, or liver or kidney weights for rats or dogs between exposure and control groups were noted. No other exposure-related lesions were observed in rats or dogs. Therefore, a free-standing LOAEL of 117 ppm in both rats and dogs for hyperplasia, inflammation, and squamous metaplasia of nasal mucosa, was identified from these studies.

4.1.2.1.2 Study II

In a subsequent inhalation study to evaluate a no-effect level for squamous metaplasia of the nasal mucosa, 15 Fischer-344 rats per sex per group were exposed to mean measured concentrations of 0, 1.1, 10.3, and 51.3 ppm n-butyraldehyde, 6 h/d, 5 d/week for 12 weeks. Evaluation for toxic effects included body weight, food consumption, organ weight, serum chemistry, histopathologic changes, ophthalmologic and neurologic examinations. No treatment-related effects were observed in any exposure group. Histopathologic findings indicated that no specific adverse effects including squamous metaplasia of the nasal, olfactory, or respiratory epithelial tissues could be attributed to n-butyraldehyde. A NOAEL of 51.3 ppm for irritation of

respiratory tract was therefore identified from this study. The subchronic NOAEL was then used as the POD to derive the chronic ReV.

4.1.3 MOA Analysis

As described in Section 3.3, the MOA for irritation, which appears to be the critical effect, is unknown. However, the responses may be associated with the crosslinking of aldehydes with proteins (Steinhagen and Barrow 1984). Because the hydrated form of an aldehyde may be responsible for protein crosslinking, the relative potency of an aldehyde may be related to the degree to which it hydrates.

4.1.4 Dose Metric

Since the key study is based on animals exposed to the parent chemical, exposure concentration of the parent chemical is the default dose metric.

4.1.5 POD for Key Studies and Critical Effects

The NOAEL of 51.3 ppm for hyperplasia, inflammation, and squamous metaplasia of nasal mucosa identified from the Union Carbide (1979) 12-week inhalation study in rats (USEPA 1988) was used as the POD to derive the chronic ReV for n-butyraldehyde. The critical effects noted in rats were considered relevant to humans, although humans may be less susceptible to the degeneration of nasal and olfactory epithelium because rats are obligate nose-breathers and the delivered dose to the nasal and olfactory epithelium is higher in rats than humans. However, the associated LOAEL for hyperplasia, inflammation, and squamous metaplasia of nasal mucosa from Study I also occurred in dogs, in addition to rats.

4.1.6 Dosimetric Adjustments

4.1.6.1 Exposure Duration Adjustments

According to the TCEQ (2012), the subchronic POD of 51.3 ppm was then adjusted from discontinuous exposure (6 h/d for 5d/week) to continuous exposure concentration using the following dosimetric adjustments:

POD_{ADJ} = POD x D / 24 x F/7

POD_{ADJ} = 51.3 ppm × 6/24 × 5/7

POD_{ADJ} = 9.16 ppm

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

4.1.6.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

Subchronic exposures to n-butyraldehyde caused hyperplasia, inflammation, and squamous metaplasia of the nasal tissues, which is considered contact site toxicity or a POE effect, so default dosimetric adjustments from animal-to-human exposure for n-butyraldehyde were conducted as a Category 1 vapor. When the critical effect is in the extrathoracic region (ET) region, the animal-to-human dosimetric adjustments will use a default DAF of 1, as recommended by the USEPA 2012 Advances in Inhalation Gas Dosimetry summary document (USEPA 2012). Accordingly, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$POD_{HEC} = POD_{ADJ}$ x default DAF

= 9.16 ppm x 1

= 9.16 ppm

4.1.7 Adjustments to the POD_{HEC} to Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

The MOA by which n-butyraldehyde produces hyperplasia, inflammation, and squamous metaplasia of nasal mucosa is assumed to produce a threshold for response, so a POD_{HEC} was determined and UFs were applied to derive the chronic ReV. The following UFs were applied to the POD_{HEC}:

- UF_H = 10 was used to account for human variation;
- UF_A = 3 was used for extrapolation from animals to humans because default dosimetric adjustments from animal-to-human exposure were conducted, which account for toxicokinetic differences but not toxicodynamic differences;
- UF_{Sub} = 3 because the rat exposure durations in the Union Carbide study were 12 and 13 weeks (i.e. ≤ 13 weeks), which is considered a subchronic exposure duration for rats (USEPA 1994)) for Study II and Study I, respectively. Additionally, as indicated in Section 3.1.6, n-butyraldehyde which has alow Kow is expected to be rapidly oxidized to butyric acid by aldehyde dehydrogenase and is not expected to accumulate in humans. Thus, a UF_{Sub} of 3 is considered sufficient;
- UF_D =3 because the noncancer database relevant to long-term exposure includes only one subchronic animal inhalation study, although multiple doses and two species (rats and dogs) were studied. No other studies are available for supporting studies. The quality of the key study is considered high; however, the confidence in the database is low to medium and thus.
- The total UF = 270.

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

The chronic ReV value was calculated by the following equation:

$$\begin{aligned}\text{Chronic ReV} &= POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D) \\ &= POD_{HEC} / (10 \times 3 \times 3 \times 3) \\ &= 9.16 \text{ ppm} / 270 \\ &= 9{,}160 \text{ ppb} / 270 \\ &= 33.93 \text{ ppb } (100.09 \text{ µg/m}^3)\end{aligned}$$

The chronic ReV values were rounded to two significant figures at the end of all calculations. The derived chronic ReV of 34 ppb (100 µg/m^3) was used to calculate the $^{chronic}ESL_{threshold(nc)}$. The $^{chronic}ESL_{threshold(nc)}$ of 10 ppb (30 µg/m^3) is based on the chronic ReV multiplied by a HQ of 0.3, then rounded to two significant figures at the end of all calculations (Table 6 below). The resulting ReV and $^{chronic}ESL_{threshold(nc)}$ are used for the evaluation of ambient air monitoring data and air permits.

Table 6. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	**Summary**
Study	Union Carbide study (USEPA 1988)
Study Population	15 Fischer-344 rats per sex per group; SD rats (20 rats/sex/group); and 4 male beagle dogs per group
Study Quality	High
Exposure Method	Via inhalation at 0, 1.1, 10.3, and 51.3 ppm (analytical concentrations) for Fischer-344 rats (Study II); and 0, 117, 482, or 1852 ppm (analytical concentrations) for SD rats and male beagle dogs (Study I)
Critical Effects	Hyperplasia, inflammation, and squamous metaplasia of the nasal tissues (nasal irritation) in SD rats and male beagle dogs
LOAEL	117 ppm in SD rats and beagle dogs (Study I, free-standing LOAEL from Study I)
NOAEL	51.3 ppm in Fischer-344 rats (Free-standing NOAEL from Study II)
POD (original animal study)	51.3 ppm
Exposure Duration	6 h/d, 5 d/week, for 13-14 weeks (Study I) and 12 weeks (Study II)
Extrapolation to continuous exposure (POD_{ADJ})	9.16 ppm
POD_{HEC}	9.16 ppm
Total UFs	270
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Sub chronic to chronic UF	3
Incomplete Database UF	3
Database Quality	Low to medium
Chronic ReV (HQ = 1)	**100 µg/m^3 (34 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**30 µg/m^3 (10 ppb)**

4.2 Carcinogenic Potential

No carcinogenicity study for n-butyraldehyde is available. Evidence for the potential carcinogenicity of n-butyraldehyde is inconclusive (NIOSH 1991, USEPA 1994). Results from short term mutagenicity testing of n-butyraldehyde are mixed. n-Butyraldehyde was negative for mutation in five strains of *Salmonella typhimurium* with or without metabolic activation up to 10 mg/plate (HSDB 2012). n-Butyraldehyde was negative for sister chromatid exchange in human lymphocytes but positive in Chinese hamster ovary cells (<9 mg/mL). The chemical was negative for sex-linked recessive lethal in Drosophila melanogaster (Dynamac Corporation 1988, as cited in USEPA 1994). Moutschen-Dahmen et al. (1976, as cited in NIOSH 1991) reported that n-butyraldehyde induces chromosomal damage and meiotic anomalies in male mice during spermatogenesis in both gavage and inhalation studies. n-Butyraldehyde is not included in International Agency for Research on Cancer (IARC) animal or human carcinogenic classification. USEPA (1994) concludes there is insufficient evidence in either humans or animals to classify n-butyraldehyde as to its potential carcinogenicity.

4.3 Welfare-Based Chronic ESL

No information was found to indicate that chronic vegetation effects result from exposure to n-butyraldehyde.

4.4 Chronic ESL and Values for Air Monitoring Evaluation

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

- Chronic ReV = 100 µg/m^3 (34 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 30 µg/m^3 (10 ppb)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{threshold(nc)}$ of 30 µg/m^3 (10 ppb) as no $^{chronic}ESL_{nonthreshold(c)}$ was derived (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is set to protect noncancer nasal lesions from chronic exposure. For evaluation of air monitoring data, the chronic ReV of 100 µg/m^3 (34 ppb) is used (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) is not used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Level

The free-standing subchronic LOAEL of 117 ppm from the Union Carbide Study I (USEPA 1988) that evaluated upper respiratory tract irritation in SD rats and beagle dogs (Tables 5) was used as the initial POD for calculation of a chronic inhalation LOAEL. No duration adjustment was made (TCEQ 2012). However, an animal-to-human dosimetric adjustment was made to the $LOAEL_{ADJ}$ to calculate a $LOAEL_{HEC}$. As indicated in Section 4.1.6.2, the critical effect (hyperplasia, inflammation, and squamous metaplasia of the nasal tissues) is considered contact site toxicity or a POE effect, so default dosimetric adjustments from animal-to-human exposure for n-butyraldehyde were conducted as a Category 1 vapor. Since, the critical effect is in the extrathoracic region (ET) region, the animal to human dosimetric adjustments will use a default DAF of 1. Accordingly, the $LOAEL_{HEC}$ was calculated using the following equation:

LOAE L_{HEC} = $LOAEL_{ADJ}$ x default DAF
= 117 ppm x 1
= 120 ppm (rounded to two significant figures)

The $LOAEL_{HEC}$ determined from animal studies, where effects occurred in animals, represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over the same duration as used in the study or longer. Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 120 ppm is provided for informational purposes only (TCEQ 2012). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose.

The margin of exposure between the chronic inhalation observed adverse effect level of 120 ppm (120,000 ppb) to the chronic ReV of 34 ppb is a factor of 3500.

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