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Acrylonitrile

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	acute exposure guideline level
AMCV	air monitoring comparison value
AMAP	Amplitude of the muscular potential
ASAP	Amplitude of the sensory potential
AUC	area-under-the-curve
BMC	benchmark concentration
BMCL	95% lower confidence limit of the BMC
^{0} C	degrees Celsius
CEO	2-cyanoethylene oxide
CN^{-1}	cyanide
CNS	central nervous system
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
$^{chronic}ESL_{threhsold(c)}$	chronic health-based effects screening level for threshold dose response cancer effect
$^{chronic}ESL_{threhsold(nc)}$	chronic health-based effects screening level for threshold dose response noncancer effects
$^{chronic}ESL_{nonthrehsold(c)}$	chronic health-based effects screening level for nonthreshold dose response cancer effects
$^{chronic}ESL_{nonthrehsold(nc)}$	chronic health-based effects screening level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based effects screening level

Acronyms and Abbreviations	Definition
EU	European Union
GD	gestation day
GSH	glutathione
h	hour
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury
HEC	human equivalent concentration
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
min	minute
MCV	Motor conduction velocity
MOA	mode of action
n	number
NAC	National Advisory Committee
NOAEL	no-observed-adverse-effect-level
OAEL	Observed adverse effect level
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment

Acronyms and Abbreviations	Definition
OSHA	Occupational Safety and Health Administration
PND	postnatal day
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
RfC	reference concentration
RGDR	regional gas dose ratio
SCV	Sensory conduction velocity
TCEQ	Texas Commission on Environmental Quality
TRI	Toxics Release Inventory
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
WOE	weight-of-evidence

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 acrylonitrile (AN). Please refer to Section 1.6.2 of the *TCEQ Guidelines to Develop Toxicty 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 AN's physical/chemical data.

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

Short-Term Values	Concentration	Notes
Acute ReV [1h] (HQ = 1.0)	1,100 µg/m^3 (500 ppb) **Short-term health**	**Critical Effect(s):** Absence of effects in human volunteers; irritation of mucous membranes and headache in workers
$^{acute}ESL_{odor}$	---	Weakly sharp garlic-onion odor
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV (HQ = 1.0)	7.1 µg/m^3 (3.3 ppb) **Long-term health**	**Critical Effect(s):** Nasal irritation-degeneration and inflammation of nasal respiratory epithelium; hyperplasia of mucous secreting cells in rats
$^{chronic}ESL_{nonthreshold(c)}$	---	**Cancer Endpoint:** Brain/CNS tumors in rats; but not likely to be carcinogenic to humans
$^{chronic}ESL_{veg}$	---	No data found

[a] AN is not monitored for by the TCEQ's ambient air monitoring program, so currently no ambient air data (i.e., peaks, annual averages, trends, etc.) are available to assess AN concentrations in Texas ambient air

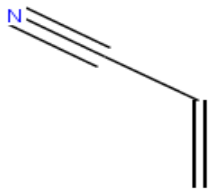
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	330 µg/m^3 (150 ppb) [a] **Short-term ESL for Air Permit Reviews**	**Critical Effect(s)**: Absence of effects in human volunteers; irritation of mucous membranes and headache in workers
$^{acute}ESL_{odor}$	---	Weakly sharp garlic-onion odor
$^{acute}ESL_{veg}$	---	No data found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	2.1 µg/m^3 (1 ppb) [b] **Long-term ESL for Air Permit Reviews**	**Critical Effect(s)**: Nasal irritation-degeneration and inflammation of nasal respiratory epithelium; hyperplasia of mucous secreting cells in rats
$^{chronic}ESL_{nonthreshold(c)}$	---	**Cancer Endpoint:** Brain/CNS and other sites tumors in rats; but not likely to be carcinogenic to humans
$^{chronic}ESL_{veg}$	---	No data found

[a] Based on the acute ReV of 1,100 µg/m^3 (500 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 chronic ReV of 7.1 µg/m^3 (3.3 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_3H_3N	ChemIDplus 2011
Chemical Structure		ChemIDplus 2011
Molecular Mass	53.06 g/mole	ACGIH 2001
Physical State	Liquid	ACGIH 2001
Color	Clear, colorless	ACGIH 2001
Odor	Mild, unpleasant odor	ACGIH 2001
CAS Registry Number	107-13-1	ACGIH 2001
Synonyms	AN, cyanoethylene, 2-propenenitrile, vinyl cyanide, carbacryl, fumigrain and ventox	ChemIDplus 2011
Solubility in water	74,500 mg/L @ 25°C	ChemIDplus 2011
Log K_{ow}	0.25	ChemIDplus 2011
Vapor Pressure	109 mm Hg @ 25°C	ChemIDplus 2011
Vapor Density (air = 1)	1.8	HSDB 2011
Density/Specific Gravity (water = 1)	0.8004	ACGIH 2001; HSDB 2011
Melting Point	-83.5°C	ChemIDplus 2011
Boiling Point	77.3°C @ 760 mm Hg	ChemIDplus 2011
Conversion Factors	1 ppm = 2.15 mg/m^3 @ 25 C 1 mg/m^3 = 0.46 ppm	ACGIH 2001

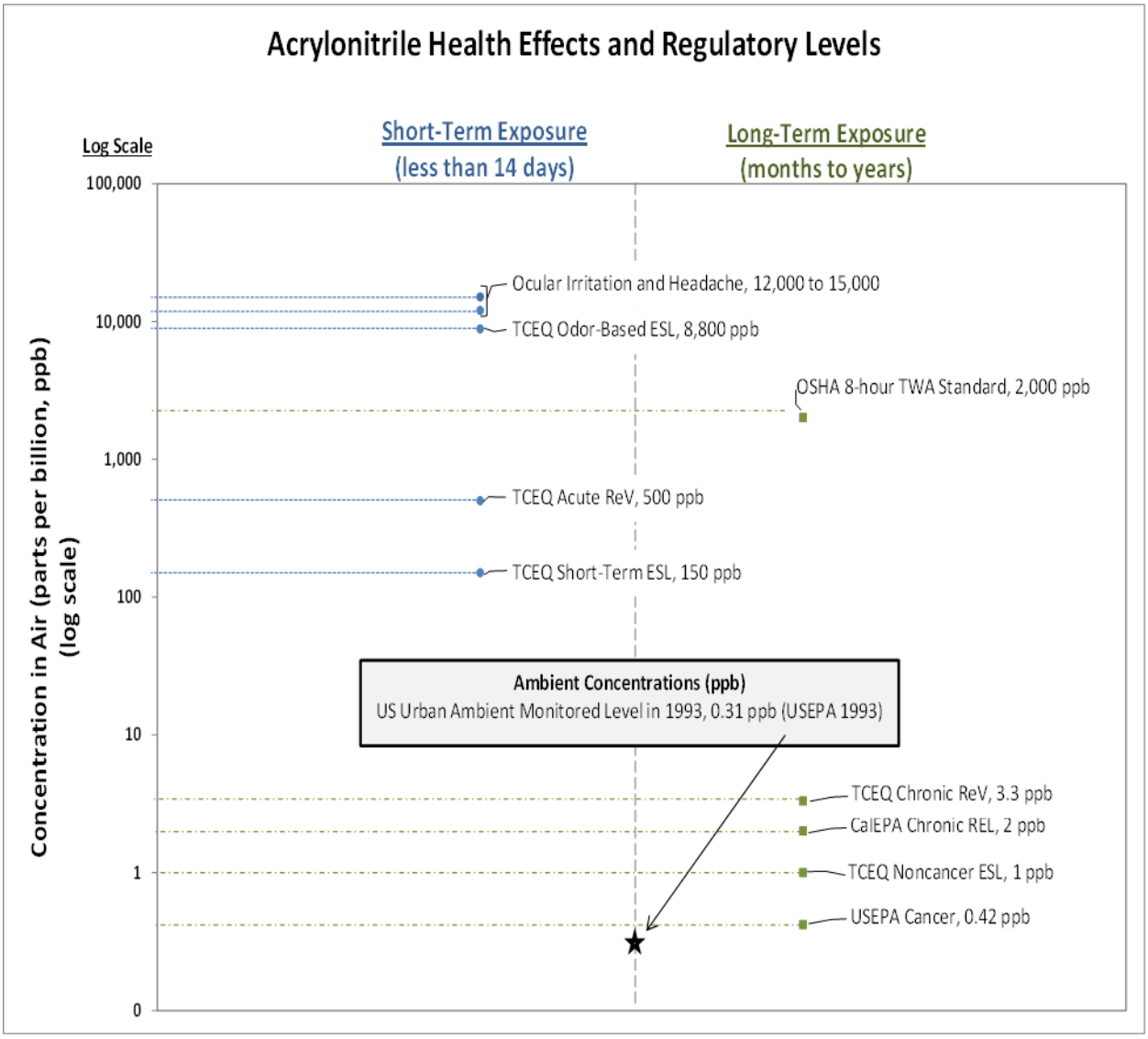


Figure 1 Acrylonitrile Health Effects and Regulatory Levels

Figure 1 compares AN's 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 Table 1 and 2 to the air concentrations associated with ocular irritation and headache, the United States Environmental Protection Agency's (USEPA) acceptable cancer risk values and chronic reference concentration (RfC) (USEPA 2002), the California Environmental Protection Agency's (CalEPA) chronic reference exposure level (REL) (OEHHA 2011) and time-weighted average (TWA) permissible exposure level set by the Occupational Safety and Health Administration (OSHA).

Chapter 2 Major Sources or Uses and Ambient Air Concentrations

2.1 Major Sources or Uses

AN is primarily a man-made chemical; it is produced from ammonia and propylene via catalytic ammoxidation in a closed system. It is also a combustion by-product from biomass (Karl et al. 2003; Yokelson et al. 2008, as cited by AN Group 2013). AN is used in the production of plastics, synthetic rubber, nitrile elastomers, AN-butadiene-styrene and styrene-AN resins and acrylic fibers, as well as an intermediate in the production of other important chemicals, such as adiponitrile and acrylamide (ATSDR 1990, ACGIH 2001, EU 2004, AEGL 2007, HSDB 2011). World-wide production of AN has been estimated at 4 to 4.5 million metric tons per year (AEGL 2007) with 3.4 million pounds (lbs) produced in the US in 1996 (NTP 2011). Primarily, AN is released into the environment through volatilization from industrial production and processing to air and wastewater. Texas is an important state for the AN industry, with the majority (~70%) of the U.S. AN monomer production occurring at two manufacturing sites in Texas (AN Group 2013). According to the USEPA's Toxics Release Inventory (TRI), in 2007, a total of about 7 million lbs of AN was released from 94 facilities, most of which (6.6 million lbs) was released by two facilities to on-site hazardous waste underground injection wells (TRI 2009, as cited in NTP 2011). The USEPA's National Toxics Inventory (USEPA 2002) indicates that Texas contributes 11% of the annual AN nationwide ambient emissions (216,012 lbs of the nationwide 2,470,178 lbs).

2.2 Background Levels of AN in Ambient Air

Measurable levels of atmospheric AN are mainly associated with industrial sources although the AN Group (2013) indicated that biomass (and perhaps other) combustion sources likely play a significant role in contributing to background levels of AN in the ambient air. The median concentration of AN for 43 measurements near AN chemical plants in the U.S. was 2.1 µg/m^3 (0.97 ppb) (Brodzinsky and Singh 1983, as cited in ATSDR 1990). The vast majority of air samples are below the detection limit, and those above the detection limit are mostly below 1 ppb (2.2 µg/m3) (AN Group 2013). The USEPA (1993, as cited in OEHHA 2001) reported mean ambient air concentration of AN at four urban locations in the US of 0.66 µg/m^3 (0.31 ppb). The Ohio EPA (2010) reported that ambient AN concentrations measured from 34 air toxics monitoring sites located in 16 Ohio Counties (from 2000-2009) ranged from 0.22 to 1.58 µg/m^3 (0.1 to 0.73 ppb). According to USEPA AirData (AN Group 2013), the highest mean ambient AN concentration of 0.213 µg/m^3 (0.097 ppb) with a maximum measured concentration of 1.54 µg/m^3 (0.7 ppb) was reported from two monitoring sites in Deer Park, Texas in 2007.

Chapter 3 Acute Evaluation

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

Inhalation of AN vapors can cause respiratory irritation and at higher levels, neurological symptoms including dizziness, weakness, headache and impaired judgment (IARC 1999).

Headache, nausea and dizziness have been reported in humans exposed to AN concentrations of 16-150 ppm for short periods (Wilson et al. 1948; Cole et al. 2008). No signs or symptoms were reported in male volunteers following exposure up to 5 ppm for 8 hours (h) (Jakubowski et al. 1987). Acute inhalation exposure studies in several laboratory animal species showed that AN exposure induced effects similar to those observed in humans. The TCEQ chose the Jakubowski et al. (1987) human volunteer study as the key study to develop the acute reference value (ReV) and effects screening level (ESL) for subjective symptoms. The key study was supported by one observational study in workers by Wilson et al. (1948) and two animal studies by Dudley and Neal (1942) and Dudley (1942).

3.1.1 Physical/Chemical Properties

AN is a highly volatile, flammable, explosive, colorless liquid with a sharp garlic-onion odor (ATSDR 1990, ACGIH 2001). It is soluble in water and many common organic solvents. It is a liquid at room temperature and during the manufacturing process, may volatilize and react quickly with other chemicals in the air. The Agency for Toxic Substances and Disease Registry (ATSDR) reports the half-life of AN in air is 5 to 50 h (ATSDR 1990) and some sources have suggested 4-18 h (NTP 2011). The main chemical and physical properties of AN are summarized in Table 3.

3.1.2 Key and Supporting Studies

This section is based on a review of current literature as well as background readings in the ATSDR (1990), IARC (1999), EU (2004), and AEGL (2007) documents which describe, in detail the acute toxicity of AN. The TCEQ used these as well as more recent publications to derive acute toxicity factors for AN.

3.1.2.1 Human Studies

3.1.2.1.1 Key Human Study (Jakubowski et al. 1987)

In a study of the efficiency of metabolism, uptake and excretion of AN in humans, Jakubowski et al. (1987) evaluated six male volunteers (aged 28-45) exposed to a nominal concentration of either 5 or 10 mg/m^3 AN vapors for 8 h with 10 min breaks at 2, 4 and 6 h. Gas chromatography was used to monitor the AN concentration every 15 min. The mean analytical concentrations monitored during experiments were 5.4 and 10.8 mg/m^3 (2.4 and 5 ppm), respectively, for the 5 and 10 mg/m^3 exposure scenarios. No subjective symptoms such as headache, nausea, or general weakness at either concentration were reported by any of the subjects during the 8-h exposure. The authors identified a free-standing no-observed-adverse-effect-level (NOAEL) of 10.8 mg/m^3 (5 ppm). The NOAEL is supported by a report of occupational exposure which indicates that exposure to AN at 10 ppm or less was without effect while exposure to 12-15 ppm in occupational workers produced mild irritation and headache regardless of exposure duration (AEGL 2007). Therefore, the free-standing NOAEL of 10.8 mg/m^3 (5 ppm) was used as the point of departure (POD) to derive the acute ReV.

3.1.2.1.2 Supporting Human Study (Wilson et al. 1948)

Wilson et al. (1948) published an observational study that described the medical problems encountered by employees of the rubber industry. In this study, the most frequently observed symptoms in workers handling AN included dull headache, fullness in the chest, irritation of mucous membranes including the eyes, nose and throat, and a feeling of apprehension and nervous irritability. Additionally, "some workmen complained of intolerable itching of the skin with no demonstrable dermatitis." These symptoms were observed in individuals exposed for 20 to 45 min to AN concentrations varying from 16 to 100 ppm. The level of 16 ppm can be considered the lowest-observed-adverse-effect-level (LOAEL) which supports the NOAEL of 5 ppm identified from the Jakubowski et al. (1987) key study.

3.1.2.2 Supporting Animal Studies

Acute AN toxicity has been extensively studied in mammals. These studies have shown that toxic effects of this chemical vary by species (Dudley and Neal 1942). Although toxic doses may vary for each species, there is a sequential series of events in all mammals that follows acute AN inhalation exposure.

3.1.2.2.1 Dudley and Neal (1942)

In a single-exposure study of a variety of animal species to AN by Dudley and Neal (1942), Osborne-Mendel rats (16/group) were exposed to 100, 130, 315, or 635 ppm, Rhesus monkeys were exposed to 65 (2 males and 2 females) and 90 ppm (2 females), groups of 2-4 cats exposed to 100, 275, or 600 ppm, groups of 2-3 albino rabbits exposed to 100, 135, 260, or 580 ppm and groups of 2-3 male and/or female dogs were exposed to 30, 65, 100, or 165 ppm AN for 4 h. Flushing or reddening of the skin, nose and feet were observed in all exposure groups. Rats exposed to as low as 100 ppm exhibited slight irritation of the mucous membranes, nasal exudates and watering of the eyes. In the same study, the only effect noted was a slight initial stimulation of respiration observed in two male and two female rhesus monkeys exposed to 65 ppm AN. Two female monkeys exposed to 90 ppm exhibited slight redness of the face and genitals and slight weakness; however, these effects disappeared 12 h after exposure. Similar results were observed in three female dogs exposed to 30 ppm (slight salivation), two female dogs exposed to 65 ppm (one in coma and another exhibited severe salivation and weakness), cats exposed to 100 ppm (salivation and slight transient redness of skin and mucosa) and albino rabbits exposed to 100 ppm (slight to marked transient effects in respiratory pattern and irritation). The study showed that slight transitory effects were observed in all tested animal species exposed to the lowest exposure concentrations. The severity of effects (from mild transitory to fatal) was increased with the exposure levels increased. Dogs were identified as the most sensitive species evaluated in this study with a LOEAL of 30 ppm for slight salivation.

3.1.2.2.2 Dudley et al. (1942)

In a subacute study, Dudley et al. (1942, as cited in AEGL 2007) exposed four rhesus monkeys to 56 ppm AN 4 h/day (d), 5 d/week for four weeks and found no evidence of toxicity.

In addition to a preference for human data (TCEQ 2012), the NOAELs/LOAELs identified from the aforementioned animal studies are higher than those from human studies and thus, were not used as the POD to derive acute toxicity values. Figure 2 (below) shows an inhalation exposure-response array for acute and subacute exposure to AN.

3.1.2.2.3 WIL Research Laboratories (2005) Study

In an acute inhalation toxicity study of AN sponsored by the Shanghai SECCO Petrochemical Company, Ltd. and SNF SAS (WIL Research Laboratories 2005), groups of 5 male and 5 female Crl:CD7(SD) albino rats (8-12 weeks old; 242-297 g) were exposed (nose-only) for 4 h to 539, 775, 871, 1006, or 1181 ppm AN (99.9 % purity). Mortality, clinical observations and body weight changes were evaluated over a 14-d observation period. All animals were subjected to a gross necropsy. The results of this study report a 4-h lethal concentration that kills 50% of the test animals (LC_{50}) values of 964 ppm for males, 920 ppm for females, and 946 ppm for combined males and females.

3.1.3 Reproductive/Developmental Toxicity Studies

The reproductive and developmental toxicities of AN have been well studied in animals and humans.

3.1.3.1 Epidemiological Studies

Cross-sectional epidemiological studies of reproductive outcomes in Chinese AN-exposed workers found an increased prevalence of adverse reproductive outcomes associated with average workplace air concentrations of 3.6 to 7.6 ppm (Dong et al. 2000a and Li 2000, Collins et al. 2003, as cited in Neal et al. 2009). Adverse outcomes with statistically significantly increased prevalence compared with unexposed workers included premature deliveries, stillbirths, sterility, birth defects and pregnancy complications. However, in a review by Neal et al. (2009), the authors indicated that although sufficient data exist to postulate an association between human AN exposure and adverse reproductive outcome, the data were deemed insufficient to establish causation (e.g., potential confounding factors or lack of exposure data). Thus, the existing epidemiological data were not used to derive toxicity values.

3.1.3.2 Animal Studies

3.1.3.2.1 Saillenfait et al. 1993

In a comparative study of relative developmental toxicities of eight aliphatic mononitriles, Saillenfait et al. (1993) exposed groups of 20-23 pregnant Sprague-Dawley (SD) rats to 0, 12, 25, 50 or 100 ppm AN (nominal concentrations) by inhalation for 6 h/d during gestational days (GD) 6-20. Animals were euthanized on day 21. Analytical concentration of AN was determined hourly using gas-liquid chromatography. The respective mean ± SD analytical concentrations for AN exposure groups were 12±0.6, 25±1.2, 51±4.4 and 98±8.9 ppm. None of the animals died during the study and there were no teratogenic effects. No adverse effects on the pregnancy rate, average number of implantations and live fetuses, or incidences of nonsurviving implants and

resorptions per litter were observed among litters exposed to AN. However, there was a statistically significant decrease in maternal absolute body weight gain, as well as fetal body weight at the three highest dose groups (25, 50 and 100 ppm). A gradual decrease in maternal body weight gain and fetal body weight was associated with increasing AN concentrations with a NOAEL of 12 ppm. The results of this study showed that AN was fetotoxic in the presence of maternal toxicity. A NOAEL of 12 ppm for decreased maternal body weight gains and fetal body weight gains were identified from this study (Table 4). However, decreases in fetal body weight gains were likely due to a simple compensating effect by smaller dams (due to decreases in maternal body weight gains) and thus, were not biologically relevant.

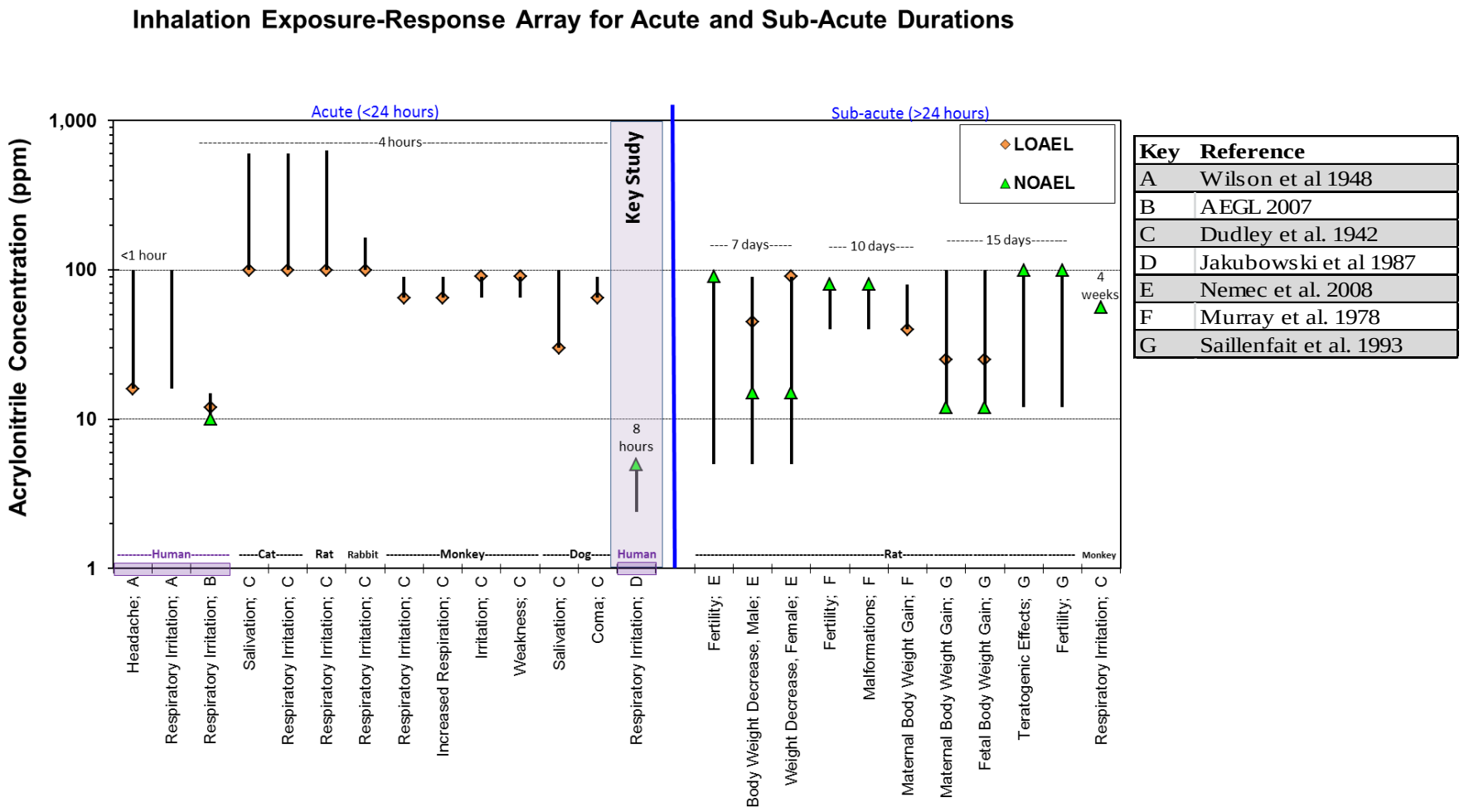
Table 4. Reproductive/developmental parameters in rats (Saillenfait et al. 1993)

Parameter	0 ppm AN	12 ppm AN	25 ppm AN	50 ppm AN	100 ppm AN
Male fetal body weight	5.95±0.28	5.79±0.28	5.64±0.36**	5.54±0.24**	5.04±0.36**
Female fetal body weight	5.66±0.36	5.51±0.27	5.37±0.28*	5.18±0.25**	4.90±0.49**
Absolute maternal body weight gain	25.1±18.2	16.1±13.5	-0.1±16 **	-7.8±13.1**	-24.3±20.1 **
Maternal body weight gain	119.1±29.9	123.4±19.7	100.5±18.7*	95.8±14.3**	65.2±22.4**

* $P < 0.05$
** $P < 0.01$

3.1.3.2.2 Murray et al. (1978)

Murray et al. (1978) conducted a teratogenicity study of 30 pregnant SD rats exposed to 0, 40, or 80 ppm AN (nominal concentrations) by inhalation for 6 h/d during GD 6-15, 5 fewer days than Saillenfait et al. (1993). The respective mean analytical concentrations for the 40 and 80 ppm exposures were 40±2 and 77±8 ppm. The results of this study show no statistically significant treatment-related signs of any single malformation during the exposure period. The pregnancy incidence, mean litter size incidence of resorptions and average fetal body measurements were unaffected (AGEL 2007). However, there was marginally increased total incidence of major malformations, including short tail, short trunk, missing ribs and delayed ossification of skull bones, omphalocele (an anterior abdominal wall defect) and hemivertebrae (a vertebra that is incompletely developed on one side) at an exposure concentration of 80 ppm compared to the control incidence ($p = 0.06$). In addition, two fetuses from different litters had a short tail and missing vertebrate in the 80 ppm-exposed group but this effect was not observed in the control or 40 ppm-exposed group. The results also showed no embryo/fetal effects were observed but maternal body weight gain was decreased at 40 and 80 ppm.



Key	Reference
A	Wilson et al 1948
B	AEGL 2007
C	Dudley et al. 1942
D	Jakubowski et al 1987
E	Nemec et al. 2008
F	Murray et al. 1978
G	Saillenfait et al. 1993

Figure 2 Exposure-Response Array for Acute and Subacute Exposure to Acrylonitrile

3.1.3.2.3 Nemec et al. (2008)

Nemec et al. (2008) completed a two-generation reproductive study after exposure of SD rats to AN. Since this study is considered a chronic study (greater than 10% of lifespan), it is described in detail in Section 4. However, body weight data after a one-week exposure are included and are informative. Briefly, SD rats (25/sex/group) were exposed via whole-body inhalation at concentrations of 0, 5, 15, 45 and 90 ppm. In F_0 males, body weights were significantly decreased after one week of exposure at 45 and 90 ppm; whereas, in F_0 females, body weights were significantly decreased after one week of exposure at 90 ppm (LOAEL of 45 ppm with a NOAEL of 15 ppm based on males). During GD 4-20, maternal body weight was significantly deceased at 90 ppm only (LOAEL of 90 ppm with a NOAEL of 45 ppm based on maternal body weight). Therefore, a decrease in body weight was observed in both male and female rats, with the males being slightly more sensitive. A NOAEL (15 ppm) and LOAEL (45 ppm) for parental systemic effects was identified from this study.

3.1.3.2.4 Weight-of-Evidence Review

In a weight-of-evidence (WOE) review, Neal et al. (2009) indicated that although sufficient data exist to postulate an association between human AN exposure and adverse reproductive outcome, the data were deemed insufficient to establish causation (e.g., potential confounding factors or lack of exposure data). Epidemiological studies do not demonstrate causality and are not sufficiently robust to be used for risk assessment. While fetotoxicity and malformations at maternally toxic levels were observed in rodent developmental studies, the existing animal inhalation studies (e.g., Saillenfait et al. 1993, Murray et al. 1978, Nemec et al. 2008) do not show any clear indication of decreased in fertility, dominant lethal, reproductive or teratogenic effects of AN exposure at doses below those producing parental toxicity. The authors concluded that the WOE evaluation does not support a concern for developmental effects from exposures to AN at levels below those producing overt maternal toxicity and does not show a significant reproductive effect or unique developmental susceptibility.

3.1.3.2.5 Conclusions

In summary, AN is not expected to be a developmental or reproductive toxicant in the absence of significant maternal toxicity. Thus, the existing animal and epidemiological data were not used to derive toxicity values for reproductive/developmental effects.

3.1.4 Potential for AN to Cause Sensitization

AN has marked dermal sensitizing properties and may cause allergic contact dermatitis. However, there are no specific human case reports or animal studies reporting that AN has potential to cause respiratory sensitization (EU 2004).

3.1.5 Mode of Action (MOA) Analysis

The primary route of exposure for AN in humans is inhalation and AN is quickly distributed amongst all tissues (AEGL 2007). This absorption is quite rapid, with an average of 52% of

inhaled AN distributed and retained in human tissues after 8 h of exposure (Jakubowski et al. 1987). Results of animal studies have shown that AN does not bioaccumulate. AN is eliminated from the body, primarily through the urine, which can account for 77-100% of the dose and has a half-life of approximately 8 h (NTP 2011).

Acute AN toxicity is considered to be directly related to its metabolism. AN is metabolized in humans and animals via two pathways. One pathway is conjugation with glutathione (GSH) and the second is epoxidation of AN catalyzed by the cytochrome p-450 isoenzyme CYP2E1 to form 2-cyanoethylene oxide (CEO). This intermediate may undergo further metabolism by either epoxide hydrolase or conjugation to glutathione (GSH) to form cyanide (CN^{-1}) (IPCS 2002, AEGL 2007).

The acute toxic effects of AN exposure appear to be irritation of the respiratory tract. The precise MOA for irritation is not known (AEGL 2007), but may include the binding of AN or CEO to cellular macromolecules or depletion of tissue GSH levels (Kirman et al. 2008). Ghanayem *et al*. (1985, as cited in Kirman et al. 2008 and AN Group 2013) and Ahmed *et al*. (1996, as cited in AN Group 2013) reported that the MOA for portal-of-entry effects following oral AN exposure (e.g., GSH depletion and gastrointestinal irritation) may be related to metabolic activation of AN by CYP450 to a reactive metabolite other than cyanide (probably CEO). However, because nasal tissue in rats has shown to have fairly high activity for metabolizing AN to CN^- (Dahl and Waruszewski 1989, as cited in Kirman et al. 2008), nasal lesions may involve the parent chemical, CEO and/or CN^{-1} (Kirman et al. 2008). AN-induced neurological effects in laboratory animals appear to involve the parent compound and the CN^{-1} metabolite (Their et al. 2000, EU 2003, AEGL 2007, Kirman et al. 2008). AN-induced convulsions, are likely due to the result of metabolically-released CN^{-1}, although the results of acute systemic toxicity studies suggested that only the early convulsion phase may be due to the oxidative metabolism of AN to CN^{-1}, and that the terminal convulsions that precede imminent death are due to the toxicity of the parent compound (Benz and Nerland 2005). Observations in cases of acute AN intoxication have led to the conclusion that CN^{-1} has been implicated as perhaps playing a larger role in human AN-intoxications than in rodents (Thier *et al*. 2000), due to differences in oxidative metabolism.

Adverse effects from acute exposure to AN vary greatly amongst animal species, which have been attributed to the differences in metabolism between species. These effects vary in degrees of severity, target organ, and critical end-points of effect. Some of the species differences in acute AN toxicity may be explained by the rate of CEO formation. For example, rats and mice appear to form CEO 1.5- and 4-fold faster, respectively, than humans (Roberts et al. 1991, as cited in AEGL 2007). Furthermore, humans have a higher rate (1.5-fold) of conjugation of CEO to GSH followed by hydrolysis of CEO by epoxide hydrolase than either mice or rats (AEGL 2007).

3.1.6 Dose Metric

Exposure data are available for the parent chemical (but not metabolite) for the inhalation key and supporting studies. Since the precise MOA of the acute toxic response is not fully elucidated

and data on other more specific dose metrics are not available (e.g. blood concentration of parent chemical, area-under-the-curve (AUC) tissue concentration of parent chemical, or putative metabolite concentrations in blood or target tissue), the exposure concentration of the parent chemical was used as the default dose metric.

3.1.7 POD for the Key Study and Critical Effect

The free-standing NOAEL of 5 ppm (analytical concentration) based on an 8-h exposure human volunteer study by Jakubowski et al. (1987) was used as the POD to derive the acute ReV and ^{acute}ESL for AN. Wilson et al. (1948) noted that at higher concentrations (16-100 ppm for 20-45 min), dull headaches, nasal and ocular irritation, discomfort in the chest, nervousness and irritability occurred, so these are the critical effects that would be expected at or above 16 ppm.

Since the Jakubowski et al. (1987) study provides only a free-standing NOAEL; there is no documented critical effect in this study. However, symptoms observed in workers such as irritation of mucous membranes and headache from the Wilson et al. (1948) occupational study may be considered critical effects for acute AN exposure.

3.1.8 Dosimetric Adjustments

According to the TCEQ Guidelines (TCEQ 2012), since the POD from the Jakubowski et al. (1987) study is based on a free-standing NOAEL of 5 ppm and there are not adequate data to define the dose-response relationship at higher doses, the concentration at the 8-h exposure will not be adjusted to 1-h exposure duration. Thus, the POD of 5 ppm is the POD_{ADJ}, as well as the human equivalent concentration (POD_{HEC}).

3.1.9 Adjustments of the POD_{HEC}

The MOA by which AN produces acute toxicity is assumed to produce 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 5 ppm: 10 for intraspecies variability (UF_H) and 1 for database uncertainty (UF_D):

- A UF_H of 10 was used to account for intraspecies variability. There is experimental evidence that indicates AN-sensitive human subpopulations may exist due to genetic polymorphisms in metabolic genes (AEGL 2007),
- A UF_D of 1 was used because the acute database for AN includes one acute inhalation study in humans (key study); one acute occupational exposure supporting study; animal inhalation exposure supporting studies in five different species; and three reproductive/developmental toxicity studies in different species (see Section 3.2). The quality of the key study is considered medium; the confidence in the acute database is medium to high.
- The total UF = 10.

Acute ReV = POD_{HEC} / (UF_H x UF_D)

= 5 ppm / (10 x 1)
= 0.5 ppm
= 500 ppb (1,100 µg/m^3) (rounded to two significant figures)

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

The acute ReV value of 500 ppb is shown with two significant figures for a final acute ReV of 500 ppb (1,100 µg/m^3). At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 150 ppb (330 µg/m^3) (Table 5).

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

Parameter	**Summary**
Study	Jakubowski et al. (1987)
Study Population	Six male volunteers (aged 28-45)
Study Quality	Medium
Exposure Method	Inhalation of either 2.4 or 5 ppm (analytical concentrations) exposure
Exposure Duration	8 h
Critical Effects	Irritation of mucous membranes and headache
LOAEL	16 ppm (Wilson 1948)
NOAEL	5 ppm (Free-standing NOAEL, Jakubowski et al. 1987)
POD	5 ppm
Extrapolation to 1 h (POD_{ADJ})	5 ppm
POD_{HEC}	5 ppm
Total uncertainty factors (UFs)	10
Interspecies UF	1
Intraspecies UF	10
LOAEL-to-NOAEL UF	N/A
Incomplete Database UF	1
Database Quality	Medium to high
Acute ReV [1 h] (HQ = 1)	**1,100 µg/m^3 (500 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**330 µg/m^3 (150 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

AN has a sharp garlic-onion odor. Odor detection threshold values of 1.56 and 8.8 ppm were reported by Stalker (1963) and Nagata (2003), respectively. Since AN does not have a pungent or disagreeable odor, an $^{acute}ESL_{odor}$ was not developed (TCEQ 2015).

3.2.2 Vegetation Effects

After a careful review of the current literature, no information regarding the vegetative toxicity of AN was located.

3.3 Short-Term ESL

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

- Acute ReV = 1,100 µg/m^3 (500 ppb)
- ^{acute}ESL = 330 µg/m^3 (150 ppb)

The short-term ESL for air permit reviews is the health-based ^{acute}ESL of 330 µg/m^3 (150 ppb) (Table 2).

3.4 Acute Inhalation Observed Adverse Effect Level

As described in Section 3.1.2.1.2, Wilson et al. (1948) reported that dull headache, fullness in the chest, irritation of mucous membranes including the eyes, nose and throat and a feeling of apprehension and nervous irritability were observed in workers exposed to AN concentrations 16 to 100 ppm for 20 to 45 min. The $LOAEL_{HEC}$ of 16 ppm or 16,000 ppb can be considered an acute inhalation observed adverse effect level.

The $LOAEL_{HEC}$ determined from human studies (where effects occurred in some individuals) represents a concentration at which it is probable that similar effects could occur in some individuals exposed to this level over the same duration as used in the key study (or longer durations). Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity. The acute inhalation observed adverse effect level is provided for informational purposes only (TCEQ 2012). The margin of exposure between the inhalation observed adverse effect level of 16,000 ppb to the ReV of 500 ppb is a factor of 32.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Local irritation, neurological, hematological, survival, and systemic effects have been observed in chronic inhalation toxicity studies with AN. Kirman et al. (2008) evaluated the WOE available from human and animal toxicity data and found that irritation and neurological effects are

consistently identified as effects for AN. Nasal irritation is the most sensitive endpoint seen in chronic inhalation studies of rats. Human data are difficult to assess in relation to establishment of a dose-response relationship for chronic toxicity. However, many of the findings in the animal studies, especially the neurological effects and irritation, reflected the reported findings in workers (EU 2004). Evidence of neurological effects in human studies from AN exposure includes an increased prevalence of subjective symptoms such as headaches and memory impairments (Kaneko and Omae 1992, as cited in Kirman et al. 2008; Muto et al. 1992), deficits in several neurobehavioral tests (Lu et al. 2005) in workers exposed to AN and deficits in sensory nerve conduction in rats (Gagnaire et al. 1998).

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

4.1.2.1 Key Animal Studies

There are two well-conducted rat studies on nasal irritation by Nemec et al. (2008) and Quast et al. (1980) that are available. Both studies administered multiple exposure levels and showed dose-effect relationships. Both the Nemec et al. (2008) and the Quast et al. (1980) studies were used by the TCEQ as key studies to develop the chronic ReV and ESL. The Quast et al. (1980) study was also used by the California EPA Office of Environmental Health Hazard Assessment (OEHHA 2001) and USEPA (1991) to derive their chronic noncancer toxicity values.

4.1.2.1.1 Nemec et al. (2008) Study

Nemec et al. (2008) conducted a two-generation reproductive toxicity inhalation study in SD rats. Groups of rats (F_0 generation, 25 rats/sex/group) were exposed to AN via whole body inhalation at 0, 5, 15, 45 and 90 ppm (nominal concentrations), 6 h/d, 7 d/week for 10 weeks pre-breeding exposure; these animals were randomly bred to produce an F_1 generation. Following weaning on postnatal day (PND) 28, animals selected to be parents from the F_1 generation were similarly exposed. Exposure of the F_1 animals to 90 ppm AN was terminated after 16 to 29 d due to excessive systemic toxicity in the males. Replication of the breeding procedure was conducted with the remaining four exposure groups in the second generation (25 rats/sex/group). The F_0 and F_1 rats were exposed for at least 10 weeks prior to mating and throughout mating, gestation and lactation until 1 d prior to euthanasia. The total direct exposure duration of ≥10 weeks (7d/week, for ≥ 70d) is considered a chronic exposure, i.e., longer than 10% of the average rat lifespan. The offspring of the F_0 and F_1 generations (F_1 and F_2 pups, respectively) were exposed to AN in utero, via milk through nursing during PND 0-28 and for F_1 pups via direct exposure following weaning. The F_1 generation was exposed indirectly for 6 weeks (transplacental during gestation and translactational while with mothers prior to weaning). They were then exposed directly after weaning and through mating, gestational and lactational periods with their own pups. The mean analytical values of AN ± SD for the 5, 15, 45 and 90 ppm groups were

5.0±0.30, 15.1±0.69, 45.3±1.51 and 89.4±3.58 ppm, respectively, for the F_0 generation and 5.0±0.25, 15.2±0.59, 45.4±1.57 and 86.5±2.45 ppm, respectively, for the F_1 generation.

Following AN exposure andrology, estrous cyclicity and testicular and ovarian histopathology were assessed for reproductive performance. In addition, histopathological evaluation of nasal tissue was conducted for all F_0 and F_1 animals in the control, 5, 15 and 45 ppm exposure groups. The results showed that, overall, there were no AN-related effects on estrous cyclicity, reproductive performance, parturition, numbers of implantation sites and unaccounted-for implantation sites, the process of spermatogenesis and reproductive organ weights and histopathology in the F_0 and F_1 animals. Results from evaluation of developmental endpoints in F_1 and F_2 offspring showed that no AN-related effects were observed in the 5 and 15 ppm exposure groups. However, a slight but statistically significant increase in relative anogenital distances in F_1 males and a decrease in body weight were observed in the 45 and 90 ppm exposure groups compared to controls. The authors, however, indicated that since there is no known mechanism for increasing male anogenital distance and the effects were not observed in the 45 ppm F_2 pups, the slight increases in anogenital distance in the 45 and 90 ppm group F_1 males were not considered AN-related toxicity.

Evidence of F_0 and F_1 parental systemic toxicity (decrements in body weights and/or food consumption) was observed for both sexes only at exposure levels of 45 and/or 90 ppm. Body weight gains for the 45 and 90 ppm F_0 males were statistically reduced relative to controls during the first three weeks of exposure, resulting in persistent and generally statistically significant body weight depressions throughout the F_0 generation. Clinical signs of irritation were observed only for the F_0 males and females exposed to 90 ppm throughout the exposure period within 1 h following completion of daily exposures, but generally did not persist to the following day. Thus, a NOAEL of 15 ppm was identified for systemic toxicity.

Histopathologic changes in nasal tissues (lesions) were observed in F_0 males and females at 45 ppm, F_1 males at 5, 15 and 45 ppm and F_1 females in the 15 and 45 ppm exposure groups. For F_1 males, although nasal lesions were observed in all three exposure groups, the lesions were statistically significant at 15 and 45 ppm but not at 5 ppm. A NOAEL and LOAEL of 5 and 15 ppm, respectively, for nasal lesions in the F_1 rats were identified from this study. Tissue damage included respiratory/transitional epithelial hyperplasia, sub-acute inflammation and squamous cell metaplasia in nasal cavity level I section and/or degeneration of the olfactory epithelium in nasal cavity level II section. The lesions showed a clear exposure-related response in incidence and severity for all three endpoints examined in F_1 males and for hyperplasia in respiratory/transitional epithelium examined in F_1 female rats (Table 6). Hyperplasia in respiratory/transitional epithelium was the most sensitive endpoints for nasal lesions. The authors further indicated that the majority of the lesions were present in the most rostral section (level I) of the nasal tissues examined. Thus, the nasal lesions were considered to be the effects of local irritation and not a systemic effect (Nemec et al. 2008). Table 6 below shows that F_1 males were more sensitive to histological changes than F_1 females at 5 ppm exposure level; however, the lesions were not statistically significant in either males or females. In addition, there were no

potential sex differences at 15 or 45 ppm. Thus, incidence data from both F_1 males and females for hyperplasia in respiratory/transitional epithelium (the most sensitive endpoint) were pooled for BMC modeling (see Section 4.2.4.1).

Table 6. Nasal Tissue Damage Observed upon Histological Examination (Nemec et al. 2008)

Number of animals with histological changes in each exposure level					
Endpoint examined in nasal level I section	**Sex**	**0 ppm**	**5 ppm**	**15 ppm**	**45 ppm**
Hyperplasia in respiratory/transitional epithelium	Male	2/10	6/10	10/10*	10/10 *
Same as above	Female	0/10	0/10	7/10*	9/10*
Same as above	Combined both male and female	2/20	6/20	17/20	19/20
Squamous metaplasia	Male	0/10	2/10	8/10 *	8/10 *
Same as above	Female	0/10	0/10	6/10*	4/10
Subacute inflammation	Male	2/10	4/10	9/10 *	9/10 *
Same as above	Female	0/10	0/10	6/10*	3/10

*Statistically significant at $p < 0.05$

4.1.2.1.2 Quast et al. (1980) Study

In an industry-supported study by Dow Chemical Company, Quast et al. (1980) exposed groups of SD rats (100 rats/sex/group) to AN via inhalation at 0, 20 and 80 ppm (nominal concentrations) for 6 h/d, 5 d/week, for two years. The respective mean ± SD analytical concentrations were 20.0±1.9 and 80.0±5.9 ppm. A significant decrease in mean body weight was observed in the rats exposed to 80 ppm. Less significant, but similar weight changes were noted in the 20 ppm females after approximately 1 month. A treatment-related effect on mean body weight was not observed in the 20 ppm males.

Results of this study showed long-term exposure of AN to rats induced statistically significant increases in cellular damage at 20 ppm in several tissues, including lung, nasal, heart, skin, liver, mammary gland, spleen and spinal cord. Of these effects, only lung and nasal tissue showed a dose-response increase in tissue damage. For lung, there was an increase over control at both the 20 ppm and 80 ppm in the incidence of pneumonia, consolidation, atelectasis (a complete or partial collapse of a lung) and edema incidence. Statistically significant degenerative and

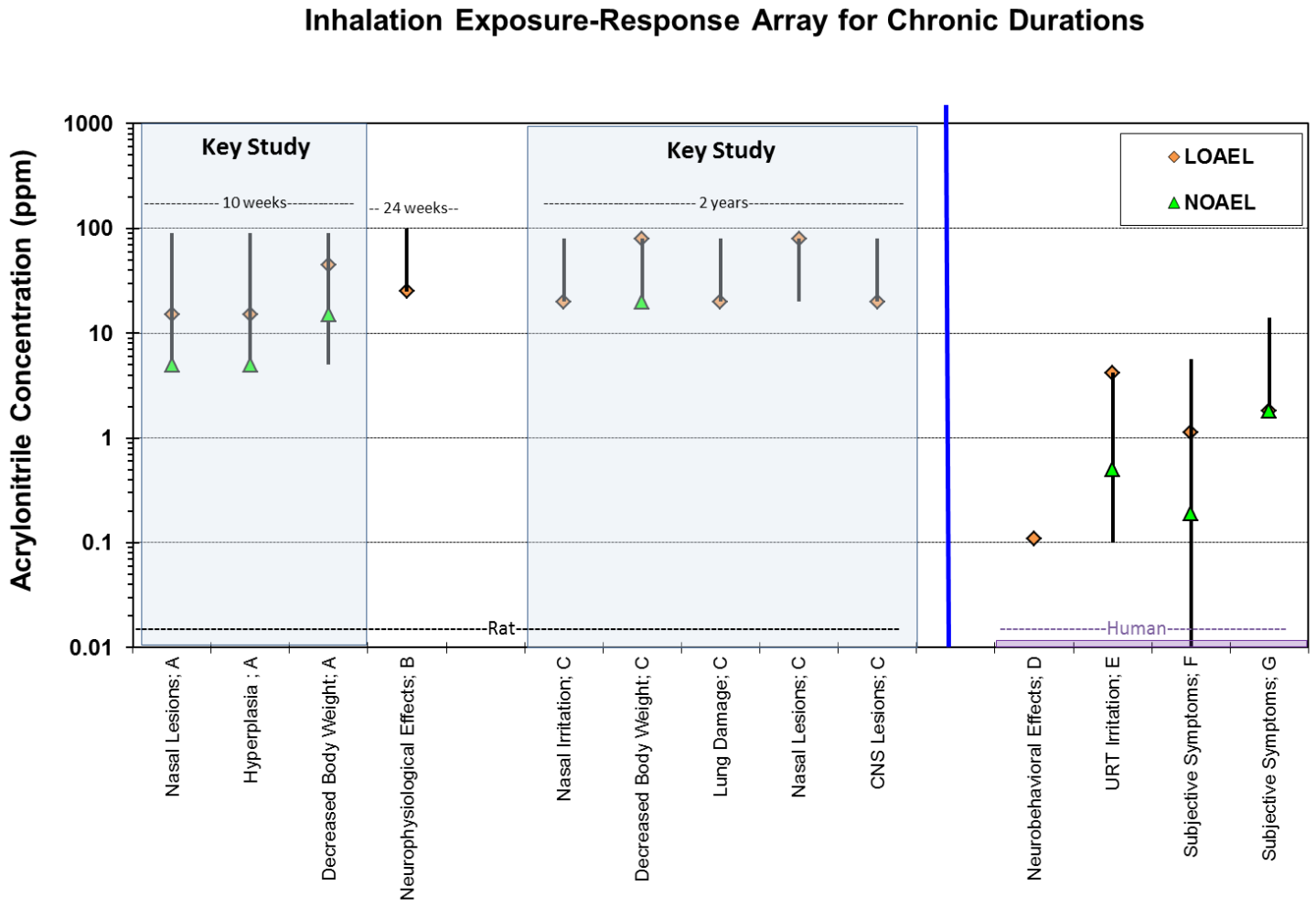
inflammatory changes were observed in the respiratory epithelium of the nasal turbinates at both exposure concentrations (see Table 7 below). These changes were interpreted to be treatment-related irritation of the nasal mucosa. In the male 20 ppm group, there was a slight but not statistically significant increase in the incidence of respiratory epithelium hyperplasia in the nasal turbinates and a statistically significant increase in hyperplasia of the mucous secreting cells. In the 20-ppm females there was a slight but not statistically significant increase in focal inflammation in the nasal turbinates and a statistically significant increase in flattening of the respiratory epithelium of the nasal turbinates. In the 80 ppm exposed male and female rats, the effects were more severe and statistically significant compared to the controls, including suppurative rhinitis, hyperplasia, focal erosions and squamous cell metaplasia of the respiratory epithelium. No treatment-related effects in the olfactory epithelium, trachea, or lower respiratory system were observed in either males or females at either concentration. A LOAEL of 20 ppm for nasal irritation, as indicated by pathological alterations in the respiratory epithelium (hyperplasia of mucus-secreting cells in males and flattening of the respiratory epithelium in females), was identified from this study. Table 7 lists incidence data of four endpoints examined in both male and female rats. The incidence data showed that males were more sensitive to hyperplasia in the nasal turbinates and mucous secreting cells than females, and females were more sensitive to focal inflammation and flattening of the nasal turbinate tissue at both 20 and 80 ppm exposure levels. Because there were potential sex differences at both exposure levels (except for hyperplasia of the mucous secreting cells in females), unlike the Nemec et al. (2008) study, incidence data from both males and females were not pooled for BMC modeling. BMC modeling was conducted for incidence data for the four endpoints examined either in males or females or both which showed most sensitive dose-response increase tissue damage (see Table 7 below).

Table 7. Pathological Alterations Observed in Rat Respiratory Epithelium (Quast et al. 1980)

Number of animals with histological changes in each exposure level			
Endpoint examined	**0 ppm**	**20 ppm**	**80 ppm**
Hyperplasia in the nasal turbinates in males [a]	0/11	4/12	10/10*
Hyperplasia in the nasal turbinates in females	0/11	2/10	5/10
Hyperplasia of the mucous secreting cells in males [a]	0/11	7/12*	8/10*
Hyperplasia of the mucous secreting cells in females	0/11	2/10	8/10*
Focal inflammation in the nasal turbinates in males	0/11	1/12	1/10
Focal inflammation in the nasal turbinates in females [a]	2/11	6/10	7/10*
Flattening of the respiratory epithelium of the nasal turbinates in males	0/11	2/12	3/10
Flattening of the respiratory epithelium of the nasal turbinates in females [a]	1/11	7/10*	8/10*

*Statistically significant at $p < 0.05$
[a] BMC modeling was conducted

Figure 3 shows an inhalation exposure-response array for chronic exposure to AN.



Key	Reference
A	Nemec et al. 2008
B	Gagnaire et al. 1998
C	Quast et al. 1980
D	Lu et al. 2005
E	Sakurai et al. 1978
F	Muto et al. 1992
G	Kaneko and Omae 1992

Figure 3 Exposure-Response Array for Chronic Exposure to Acrylonitrile

4.1.2.2. Supporting Epidemiological Studies

Several cross-sectional studies of occupational AN exposure have been conducted in Japan and China. Acrylic fiber workers were examined for subjective symptoms, physical signs, clinical chemistry and/or neurological effects. Local irritation and neurological effects are the main chronic effects found to be associated to AN-exposure in several occupational studies. For example, increased prevalence of subjective symptoms was associated with average workplace air concentrations of 1.13 ppm (Muto et al. 1992), and 1.8 ppm (Kaneko and Omae 1992). Deficits in the neurobehavioral tests were associated with average workplace air concentrations of 0.11 ppm for a group of workers designated as monomer workers and 0.91 ppm for a group of workers designated as fiber workers (Lu et al. 2005). The lowest LOAEL for neurobehavioral effects among these studies is the LOAEL of 0.11 ppm identified from the Lu et al. (2005) study (see below). Because of potential limitations in the available human epidemiological studies (e.g., lack of reliable exposure data, difficulty assessing a dose-response relationship, limitations in study designs and potential confounders), the TCEQ determined to not use these epidemiological studies to develop the chronic ReV for AN.

4.1.2.2.1 Sakurai et al. (1978) Study

Sakurai et al. (1978) performed a cross-sectional health examination in 102 male workers exposed to AN in six acrylic fiber manufacturing factories and 62 matched controls in Japan. The six factories workers were classified into three groups (A, B and C) according to their level of AN exposure. The mean 8-h time-weighted-average (TWA) AN concentrations, measured from spot samples collected by personal samplers, were 0.1, 0.5, and 4.2 ppm, respectively, for these three groups. No meaningful differences in mean clinical chemistry parameters were found between exposed workers and controls. Workers experienced irritation of eye and upper respiratory tract when exposed to high concentrations of AN. However, the slightly higher prevalence was not statistically significant compared to controls. The authors acknowledged that higher prevalence in AN workers could have been related to examiners bias.

4.1.2.2.2 Muto et al. (1992) Study

Muto et al. (1992) conducted a cross-sectional health examination of 157 male workers who had been exposed to AN for an average of 17 years in seven Japanese acrylic fiber manufacturing plants and 537 matched controls in Japan. The seven factories included the six factories studied in the Sakurai et al. (1978). TWA exposure levels were calculated for each worker using area sampling data and time studies. Personal air samples were collected for 142 of the 157 exposed workers. Overall, the TWA AN concentrations for the exposed workers were 0.53 ± 0.52 ppm (range, 0.01–2.80 ppm) and personal air concentrations were 0.62 ± 0.90 ppm (range, 0.01–5.70 ppm). No statistically significant increases in the prevalence of physical signs or abnormal values in clinical chemistry variables were found in AN-exposed workers. The results suggest that AN levels of ≤ 0.53 ppm do not cause subjective symptoms.

The exposed workers were further classified into two exposure groups, group A and B, by measured AN levels. Mean TWA and personal air concentrations for group A were 0.27 and 0.19

ppm, respectively. Mean TWA and personal air concentrations for group B were 0.84 and 1.13 ppm, respectively. No statistically significant increases in the prevalence of subjective symptoms were found in the group A. Statistically significantly increased prevalence of subjective symptoms (e.g., heaviness of stomach, poor memory, irritability, reddening of conjunctiva, and eye pain or lacrimation) was observed in group B. A LOAEL of 0.84 ppm (mean TWA) or 1.13 ppm (personal air concentrations) was identified from this study. Since historical measurements of air concentrations were not available, the identified LOAEL may not reflect the actual AN concentrations workers were exposed.

4.1.2.2.3 Kaneko and Omae (1992) Study

A cross-sectional study of subjective symptoms was performed in seven Japanese acrylic fiber manufacturing factories in Japan. The study population included 504 AN-exposed workers and 249 reference workers. Based on the measured AN concentrations in the workplace, the exposed workers were classified into three exposure groups. AN levels in the workplaces were measured on two consecutive days in each factory. The mean levels of AN concentration were 1.8, 7.4, and 14.1 ppm in low (L)-, medium (M)-, and high-level (H) groups, respectively. The corresponding averages of length of AN exposure were 5.6, 7.0, and 8.6 years for L-, M- and H-group. Health status was assessed among all the workers using the Japanese version of the Cornell Medical Index with additional questions. Prevalence of neurotic traits (defined using Fukamachi's criteria) was slightly higher among the AN-exposed workers of any group compared to each group's own reference workers, but the differences were not statistically significant. Subjective symptoms with significantly higher prevalence in the AN-exposed groups included headaches, hard to speak distinctly due to tongue trouble, choking lump in the throat, fatigue, general malaise, heavy arms, and heavy sweating. The numbers of subjective symptoms that were significantly more prevalent in exposed workers were as follows: 8 in group L, 19 in group M, and 14 in group H. The prevalence of "often feel a choking lump in the throat," had a tendency to increase with increasing length of exposure to AN in all factories and in the group L. A LOAEL of 1.8 ppm for subjective symptoms was identified from this study.

4.1.2.2.4 Lu et al. (2005) Study

Lu et al. (2005) conducted a cross-sectional study of neurobehavioral performance in Chinese acrylic fiber workers. The subjects included 81 workers in the AN-monomer department, 94 workers in the acrylic fibers department and 174 workers in the administrative or embroidery departments with no AN exposure. Periodic short-term area sampling between 1997 and 1999 indicated that the geometric means of AN exposure were 0.11 ppm (range 0.00-1.70 ppm for 390 samples) in the monomer department and 0.91 ppm (range 0.00-8.34 ppm for 570 samples) in the fiber department; however, no personal sampling data were collected. Mean durations of employment were not reported for the exposed groups. Monomer workers were also potentially exposed to CN^{-1} and fiber workers to methyl methacrylate and heat, but levels of exposure to these possible confounders were not monitored. The World Health Organization (WHO)-recommended Neurobehavioral Core Test Battery (NCTB), including seven sets of tests to evaluate neurobehavioral functions.

The results of the study showed that exposure to AN was related to adverse effects (e.g., increases in mood states and/or decreases in performance) for some components of the NCTB tests, indicating neuropsychological impairment. Scores from some tests were statistically significantly different from controls in analyses of covariance that took into account age, sex and education level. Additionally, some of the poor performances in tests were related to exposure duration. A LOAEL of 0.11 ppm for performance deficits in neurobehavioral tests of mood, attention and speed, auditory memory, visual perception and memory and motor steadiness ($p<0.05$) was identified from this study. However, there are several important limitations of the study such as: the exposure data was based on periodic area sampling during 1997 to 1999, no contemporaneous personal monitoring data were available, no dose-response was observed (i.e., the largest effects on neurobehavioral measures were observed in the low AN exposure group of the monomer department) , all tested subjects were volunteers and co-exposure to CN^{-1} and methyl methacrylate occurred among different sets of the exposed workers, but not among the controls. The potential limitations and confounders may affect the sensitivity of the scale in assessing neurobehavioral effects in the Lu et al. (2005) study (Kirman et al. 2008).

4.1.2.3 Supporting Animal Study (Gagnaire et al. 1998)

In a subchronic study for neurophysiological effects by Gagnaire et al. (1998), motor and sensory conduction velocities (MCV and SCV, respectively) and amplitudes of the sensory and motor action potentials (ASAP and AMAP) of the tail nerve in male SD rats were studied. Groups of rats (12/group) were exposed by inhalation (whole body) to 0, 25, 50 and 100 ppm of AN vapors for 6 h/d, 5 d per week, for 24 weeks. Rats exposed to AN exhibited time- and concentration-dependent decreases in MCV, SCV and ASAP, which were partially reversible after 8 weeks of recovery. Body weight gain in the 100 ppm group was significantly lower (11%) than in controls at the end of 24 week. Statistically significant deficits in SCV were observed in all exposure groups. A free-standing LOAEL of 25 ppm was identified for reduction in SCV from this study.

4.1.3 MOA Analysis and Dose Metric

The MOA for chronic nasal lesions is similar to the MOA for acute effects discussed in Section 3.1.5. Since the precise MOA of the toxic response is not fully elucidated and data on other more specific dose metrics are not available, the exposure concentration of the parent chemical was used as the default dose metric.

4.1.4 POD for Key Studies and Critical Effects

The TCEQ performed BMC modeling using USEPA BMD software (version 2.2) for data (Table 8 and 9) reported from the Nemec et al. (2008) and Quast et al. (1980) key studies (see Section 4.2.1). Data were used to predict 95% lower confidence limits on the BMCs using dichotomous models. A default BMR of 10% was selected for extra risk (BMC10) and BMCL10.

4.1.4.1 BMC Modeling for the Nemec et al. (2008) Key Study

Nemec et al. (2008) observed histological changes in the nasal tissues of the F1 adult rats after 10 weeks pre-breeding exposure to AN. As indicated in Section 4.1.2.1.1, BMC modeling was conducted for combined incidence data examined in F1 males and females for hyperplasia in respiratory/transitional epithelium.

Table 8 below and Table A-1 in Appendix A provide BMC modeling results for hyperplasia in respiratory/transitional epithelium in combined F1 males and females with 95% confidence (i.e., goodness of fit p-value and scaled residual values did not imply rejection at the 5% significance level and the model was not over-parameterized). After running all available models, the Multistage, Weibull and Quantal models for hyperplasia in respiratory/transitional epithelium in F1 male rats resulted in the lowest AIC (69.16), an acceptable p-value that was greater than 0.1 (i.e., 0.2443) and a $BMCL_{10}$ of 0.919 ppm (Table 8). The $BMCL_{10}$ of 0.919 ppm was used as the POD to derive chronic ReV and ^{chronic}ESL.

Table 8. BMC Modeling Results Based on Incidence Data (Nemec et al. 2008)

Dichotomous Model	AIC	P-value	Scaled residuals	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma Multi-Hit	71.13	0.0875	< |2|	1.52	0.921
Logistic	73.15	0.0005	< |2|	3.048	2.20
Log-Logistic	69.12	0.3394	< |2|	2.872	1.105
Log Probit	69.67	0.2279	< |2|	2.733	1.019
Multistage	69.16	0.2443	< |2|	1.295	0.919
Probit	75.84	0.0031	< |2|	3.408	2.535
Weibull	69.16	0.2443	< |2|	1.295	0.919
Quantal	69.16	0.2443	< |2|	1.295	0.919

χ^2 P-Values >0.1 indicate a significant fit

4.1.4.2 BMC Modeling for Quast et al. (1980) Key Study

BMC modeling was conducted for incidence data for four endpoints examined in the Quast et al. (1980) study (Table 9). Tables B-1 to B-4 in Appendix B provide BMC modeling results for all models that adequately modeled the experimental data with 95% confidence. Tables B-1 to B-4

also provides BMC_{10} and $BMCL_{10}$ values for each model as well as summary tables of modeling results. After running all available models for each endpoint, the Log-Logistic model for flattening of the respiratory epithelium of the nasal turbinates in female rats and hyperplasia of mucus-secreting cells in male rats resulted in the lowest $BMCL_{10}$ of 0.564 and 0.777 ppm, respectively (Table 9). All modeling results including graphs are shown in Appendix B. Both the $BMCL_{10}$ of 0.564 and 0.777 ppm were used as the POD to derive chronic ReV.

Table 9. BMC Modeling Results Based on Incidence Data (Quast et al. 1980)

Endpoint examined	Best-fitting Model	AIC	χ^2 P-value	Scaled residuals	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Hyperplasia in the nasal turbinates in male rats	Weibull	19.28	0.994	< |2|	12.134	2.961
Hyperplasia of mucus-secreting cells in male rats	Log-Logistic	28.42	0.9429	< |2|	1.778	0.777
Focal inflammation in the nasal turbinates in female rats	Log-Logistic	40.75	0.4185	< |2|	3.472	1.247
Flattening of the respiratory epithelium of the nasal turbinates in female rats	Log-Logistic	34.49	0.441	< |2|	1.533	0.564

χ^2 P-Values >0.1 indicate a significant fit

4.1.5 Selection of POD and Critical Effect

BMC modeling results (Table 8) showed that the $BMCL_{10}$ of 0.919 ppm based on the incidence data for respiratory/transitional epithelium hyperplasia in rats was identified from the Nemec et al. (2008) key study. In addition, BMC modeling results (Table 9) showed that the $BMCL_{10}$ of 0.564 and 0.777 ppm, based on the incidence data for flattening of the respiratory epithelium of the nasal turbinates in female rats and hyperplasia of mucus-secreting cells in male rats, respectively, were identified from the Quast et al. (1980) key study. Thus, the nasal lesions are a critical effect and these $BMCLs_{10}$ were used as the POD for nasal lesions to derive their respective chronic ReV and ^{chronic}ESL. TCEQ notes that since there are physiological differences between a rat nose and a human nose, the critical effects of nasal lesion observed in rats may be very conservative for humans.

4.1.6 Dosimetric Adjustments

4.1.6.1 POD from the Nemec et al. (2008) Study

4.1.6.1.1 Duration Adjustment

The POD of 0.919 ppm based on a $BMCL_{10}$ derived using nasal tissue damage for male and female rats combined was derived from the Nemec et al. (2008) study. The animals were exposed for 6 h/d, 7 d/week, thus the following calculation was applied to adjust for constant exposure to obtain an adjusted POD based on respiratory effects (POD_{ADJ}):

POD_{ADJ} = 0.919 ppm x 6 h/24 h x 7 d/7 d = 0.2298 ppm

4.1.6.1.2 POD Human Equivalent Concentration

Since the POD for the key study (Nemec et al. 2008) was based on SD rat models, a rat-to-human adjustment was applied to calculate the POD human equivalent concentration (POD_{HEC}). The critical effects (nasal lesions) were seen in the nasal cavity and thus, were considered to be the effects of local irritation which is contact site toxicity or a POE effect in the extrathoracic (ET) region. Thus, AN is considered a Category 1 gas and the default dosimetric adjustments from animal-to-human exposure was conducted based on updated animal-to-human dosimetric recommendations in USEPA (2012). The default regional gas dose ratio for the ET region ($RGDR_{ET}$) is 1.

For Category 1 gases, the default dosimetric adjustment from animal-to-human exposure is conducted using the following equation:

$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$
=0.2298 ppm x 1
=0.2298 ppm

4.1.6.2 PODs from the Quast et al. (1980) Study

4.1.6.2.1 POD Derived Based on Female Rat Model

The POD of 0.564 ppm based on a $BMCL_{10}$ derived using BMC modeling of flattening of the respiratory epithelium of the nasal turbinates in female rats was identified from the Quast et al. (1980) key study. The animals were exposed for 6 h/d, 5 d/week, thus the following calculation was applied to adjust for constant exposure to obtain an adjusted POD based on respiratory effects (POD_{ADJ}):

POD_{ADJ} = 0.564 ppm x 6 h/24 h x 5 d/7 d = 0.1 ppm

Since the POD of 0.564 ppm was based on SD rat models, a rat-to-human adjustment was applied to calculate the POD_{HEC}. The critical effects (flattening of the respiratory epithelium) were seen in the nasal turbinates and thus, were considered to be the effects of local irritation in the ET region and not a systemic effect. Thus, AN is considered a Category 1 gas and the default dosimetric adjustments from animal-to-human exposure was conducted based on updated animal-to-human dosimetric recommendations in USEPA (2012). The default regional gas dose ratio for the ET region ($RGDR_{ET}$) is 1.

For Category 1 gases, the POD_{HEC} was calculated using the following equation:

$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$
$= 0.1 \text{ ppm} \times 1$
$= 0.1 \text{ ppm}$

4.1.6.2.2 POD Derived Based on Male Rat Model

The POD of 0.777 ppm based on a $BMCL_{10}$ derived using hyperplasia of mucus-secreting cells in male rats was identified from the Quast et al. (1980) key study. The animals were exposed for 6 h/d, 5 d/week, thus the following calculation was applied to adjust for constant exposure to obtain a POD_{ADJ}:

$POD_{ADJ} = 0.777 \text{ ppm} \times 6 \text{ h}/24 \text{ h} \times 5 \text{ d}/7 \text{ d} = 0.139 \text{ ppm}$

Since the POD of 0.777 ppm was based on SD rat models, a rat-to-human adjustment was applied to calculate the POD_{HEC}. The critical effects (hyperplasia of mucus-secreting cells in nasal cavity) were considered to be the effects of local irritation and not a systemic effect. Thus, AN is considered a Category 1 gas and the default dosimetric adjustments from animal-to-human exposure was conducted based on updated animal-to-human dosimetric recommendations in USEPA (2012). The default regional gas dose ratio for the ET region ($RGDR_{ET}$) is 1.

For Category 1 gases, the POD_{HEC} was calculated using the following equation:

$POD_{HEC} = POD_{ADJ} \times RGDR_{ET}$
$= 0.139 \text{ ppm} \times 1$
$= 0.139 \text{ ppm}$

4.1.6.3 Selection of POD_{HEC}

The POD_{HEC} of 0.1 ppm, derived based on a $BMCL_{10}$ derived using BMC modeling of flattening of the respiratory epithelium of the nasal turbinate's in female rats was identified from the Quast et al. (1980) key study, is the lowest POD_{HEC} among those three derived (see Section 4.1.6.1, 4.1.6.2 above). Thus, the POD_{HEC} of 0.1 ppm was chosen to derive chronic ReV and $^{chronic}ESL_{threshold(nc)}$.

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

The MOA by which AN produces respiratory toxicity is assumed to produce a threshold for response, so the UFs were applied to POD_{HEC} to derive the chronic ReV. The following UFs were applied to the POD_{HEC} of 0.1 ppm (total UFs = 30):

- $UF_H = 10$ to account for human variation because the critical effects (nasal lesions) seen in rat nasal cavity were considered local irritation and not a systemic effect. The use of nasal lesions observed in rats as the critical effects for humans is considered conservative. However, because the nasal lesions were overt histopathology lesions, and not just

irritation, a peer review panel of AN risk assessment (Haber and Patterson 2005) recommended that a UF_H of 10 should be used.

- UF_A = 3 for the uncertainty of interspecies toxicodynamic variability, because the animal-human differences in toxicokinetics were largely accounted for through the use of the default dosimetric adjustment from animal-to-human exposure.
- UF_{Sub} = 1 because the exposure duration of F1 rats (≥ 10 weeks of direct exposure) conducted in the Nemec et al. (2008) subchronic study represented greater than 10% of the animal life, thus represented chronic exposure (see Section 4.2.1.1); and the Quast et al. (1980) study was a 2-year chronic study.
- UF_D = 1 because the chronic noncancer database includes one chronic inhalation key study in the rat (Quast et al. 1980), one two-generational reproductive toxicity and nasal irritation key study in the rat (Nemec et al. 2008), one subchronic inhalation neurotoxicity supporting study and numerous epidemiological studies for neurologic, reproductive/developmental and other effects in AN-exposed workers. The quality of two key studies is considered high; and the confidence in the database is high.

4.1.8 Possible Child/Adult Differences

As described in Section 3.1.5 and 4.1.3, acute or chronic toxic effects have been associated with inhibition of GSH-mediated detoxification of AN, transformation to CEO and CN^{-1} and oxidative stress. Differences in enzyme activities (e.g., epoxide hydrolase), pool sizes of reactive oxygen scavengers or GSH between child and adult stages may result in life stage differences in susceptibility to AN toxicity. For example, epoxide hydrolase activity in fetal tissue is about 30-40% of that in adults (Pacifici et al. 1983). The relative lower epoxide hydrolase activity for detoxification in human fetus may increase susceptibility in early life to toxic effects from AN exposure.4.1.9 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

The chronic ReV values were calculated by the following equation:

$$\begin{aligned}\text{Chronic ReV} &= POD_{HEC} / (UF_H \times UF_A \times UF_{Sub} \times UF_D) \\ &= POD_{HEC} / (10 \times 3 \times 1 \times 1) = POD_{HEC} / 30 \\ &= 0.1 \text{ ppm} / 30 = 100 \text{ ppb} / 30 = 3.3 \text{ ppb } (7.1 \text{ µg/m}^3)\end{aligned}$$

The chronic ReV value was rounded to two significant figures at the end of all calculations. The derived chronic ReV of 3.3 ppb (7.1 µg/m^3) based on the female rat model from the Quast et al. (1980) study was used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 1 ppb (2.2 µg/m^3) (Table 10 below). The resulting ReV and $^{chronic}ESL_{threshold(nc)}$ are used for the evaluation of ambient air monitoring data and air permits, respectively.

Table 10. Derivation of the Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

Parameter	Summary
Study	Quast et al. (1980) chronic study
Study Population	10-12 SD female rats per exposure group
Study Quality	High
Exposure Method	Via inhalation at 0, 20 and 80 ppm
Critical Effects	Flattening of the respiratory epithelium of the nasal turbinates in females
LOAEL	20 ppm
NOAEL	Not available
POD (original animal study)	0.564 ppm ($BMCL_{10}$)
Exposure Duration	6 h/d, 5 d/week, for 2 years
Extrapolation to continuous exposure (POD_{ADJ})	0.1 ppm
POD_{HEC}	0.1 ppm (100 ppb)
Total UFs	30
Interspecies UF	3
Intraspecies UF	10
LOAEL UF	Not applicable
Sub chronic to chronic UF	Not applicable
Incomplete Database UF *Database Quality*	1 High
Chronic ReV (HQ = 1)	**7.1 µg/m^3 (3.3 ppb)**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**2.1 µg/m^3 (1 ppb)**

4.1.10 Comparison of Various Chronic Toxicity Values

Table 11 is a comparison of noncarcinogenic chronic toxicity values derived by other federal and state agencies. The derived chronic ReV (7.1 µg/m^3), due to using a default $RGDR_{ET}$ of 1 as recommended by USEPA (2012), is slightly higher than chronic toxicity values derived by USEPA (1991) and CalEPA OEHHA (2001). The derived chronic ReV is higher than a chronic AAL (30 µg/m^3) established by the NCSAB (2010). However, the North Carolina Department of

Environmental and Natural Resources recommends an averaging time of 24 h for this chronic AAL.

Table 11. Comparison of AN Chronic Noncancer Toxicity Values

	Chronic Toxicity Value	Total UFs	$POD_{[HEC]}$	Key Study
ReV (TCEQ)	7.1 µg/m^3 (3.3 ppb)	30	0.215 mg/m^3 (0.1 ppm) ($BMCL_{10}$)	Quast et al. 1980
RfC (USEPA 1991)	2 µg/m^3	1,000	1.9 mg/m^3 ($NOAEL_{[HEC]}$)	Quast et al. 1980
REL (OEHHA 2001)	5 µg/m^3 (2 ppb)	30	$BMCL_{05}$ 1.5 ppm	Quast et al. 1980
24-h AAL (NCSAB 2010)	30 µg/m^3	10	0.27 mg/m^3 (POD_{ADJ})	Muto et al. (1992)

4.1.10.1 USEPA (1991)

The USEPA's Integrated Risk Information System (IRIS) (USEPA 1991) derived an inhalation RfC of 2 µg/m^3 (0.92 ppm) for AN. The RfC is based on the findings of Quast et al. (1980), who established the lowest exposure concentration (i.e., 20 ppm, duration-adjusted to $LOAEL_{HEC}$) as a LOAEL for treatment-related hyperplasia of mucous-secreting cells. The $LOAEL_{HEC}$ (1.9 mg/m^3) was divided by a combined UF of 1,000 (UF_H = 10, UF_A = 3, UF_L = 3, and UF_D = 10) to derive the RfC.

4.1.10.2 OEHHA (2001)

OEHHA (2001) derived a chronic reference exposure level (REL) based on the Quast et al. (1980) study using the cumulative gamma distribution model in the USEPA BMDS software. An averaged $BMCL_{05}$ of 1.5 ppm of resulting $BMCL_{05}$ values from four pathological alterations endpoints (see Table 7) was chosen as the POD. The RGDR adjustment and appropriate UFs were applied to calculate an inhalation REL of 2 ppb (5 µg/m^3). The $BMCL_{05}$ was divided by a combined UF of 30 (UF_H = 10, UF_A = 3, and UF_L = 1) to derive the RfC.

4.1.10.3 NCSAB (2010)

The North Carolina SAB has re-assessed and established a noncancer chronic acceptable ambient level (AAL) of 0.03 mg/m^3 (30 µg/m^3) in 2010. The chronic AAL is based on the Muto et al. (1992) cross-sectional study of 157 exposed and 537 unexposed workers in seven Japanese acrylic fibers factories. A NOAEL of 0.53 ppm (1.15 mg/m^3) for mucous membrane irritation was used a POD. A POD_{ADJ} of 0.27 mg/m^3 was divided by a total UF of 10 (UF_H = 10) to derive the AAL.

4.2 Carcinogenic Potential

4.2.1 Mutagenicity and Genotoxicity

AN is weakly mutagenic in reverse mutation assays in several strains of *Salmonella typhimurium*, the effect generally requiring the presence of metabolic activation. AN or its reactive metabolite CEO yielded positive results in *in vitro* mutation assays using bacteria, fungi and insect cells, as well as animal and human cell cultures (Woutersen 1998, NTP 2011). These studies have demonstrated that AN can induce gene mutations, chromosome aberrations, unscheduled DNA synthesis and cell transformation. However, *in vivo* results were mostly negative (Leonard et al. 1999). The mutagenicity/genotoxicity of AN is likely mediated primarily by CEO, a direct-acting mutagen, which may be implicated in the carcinogenicity of AN. While AN has been shown to be weakly mutagenic in *in vitro* systems, indicative of genotoxic potential, these findings are not reliably reflected *in vivo*. EU (2004) suggests that AN or CEO do not reach target tissues *in vivo*, possibly due to the detoxification of the epoxide metabolite CEO via GSH conjugation, which may not exist in *in vitro* test systems.

4.2.2 Carcinogenic WOE

AN has been proven a potent multiple-site carcinogen in rats and mice, however, there is a lack of evidence that it is a carcinogen in humans (refer to Section 4.2.2.2 Epidemiological Studies).

4.2.2.1 Animal Studies

In animals, chronic inhalation studies provide convincing evidence that AN caused an increase in tumors in the brain, Zymbal's gland and mammary glands in rats exposed for two years (Quast et al. 1980, Maltoni et al. 1988). The tumors of the CNS appear to be the predominant tumor type observed in the rat bioassays.

4.2.2.1.1 Quast et al. 1980 Study

In the Quast et al. (1980) study, a treatment-related statistically significant tumorigenic response was detected in male and female rats exposed to 80 ppm in two cell types of the brain/CNS (astrocytomas and glial cell proliferation) and the ear canal gland (Zymbal's's gland). The glial cell proliferation was considered to be a microscopic change suggestive of early tumorigenesis. Brain tumors were observed in males exposed to 80 ppm of AN and in females at 20 and 80 ppm. A dose-response relationship was observed in the brain/CNS and Zymbal's's gland (Table 12). The authors concluded that the CNS tissue appeared to be the most sensitive organ for tumors following AN exposure in both male and female rats. A free-standing LOAEL of 20 ppm for brain/CNS tumors in female rats was identified from this study. However, to better characterize the neoplasms, Kolenda-Roberts et al. (2012) evaluated nine brain tumors (astrocytomas) diagnosed from a 2-year AN drinking-water study using immunohistochemical markers. The results indicate that all AN-induced tumors were identified as malignant microglial tumors and no astrocytomas were observed. The authors further indicate that since astrocytomas are the most common human brain tumors in adult rats, the characterized malignant microglial tumors in rats may not be relevant to humans.

Table 12. Incidences of Tumors in Rats (Quast et al. 1980)

Number of animals with tumor response in each exposure level				
Tumor site	**Sex**	**0 ppm**	**20 ppm**	**80 ppm**
Brain/CNS (astrocytomas or glial cell proliferation)	Male	0/100	4/99	22/99*
Same as above	Female	0/100	8/100*	20/100*
Zymbal's gland (benign or malignant)	Male	2/96	4/93	11/82*
Same as above	Female	0/100	1/100	11/100*
Mammary gland	Male	--	--	--
Same as above	Female	9/100	7/100	20/100*
Tongue (papilloma or carcinoma)	Male	1/96	0/14	7/89*
Same as above	Female	--	--	--
Intestine	Male	4/100	3/100	17/100*
Same as above	Female	--	--	--

*Statistically significant at $p < 0.05$

4.2.2.1.2 Maltoni et al. 1988 Study

Maltoni et al. (1988) conducted cancer bioassays in SD rats exposed to AN by inhalation. In the first experiment, 30 rats/sex/group were exposed to 0, 5, 10, 20 and 40 ppm AN for 4 h/d, 5 d/week for 52 weeks. Systematic and standardized histopathologic examinations were performed on each animal. Results showed that a statistically significant but not dose-related increase in the percentage of animals bearing malignant tumors and in the number of total malignant tumors per 100 animals was observed in several exposure groups. However, no statistically significant increases in the incidences of encephalic gliomas, forestomach tumors, Zymbal's gland carcinomas, or mammary tumors were observed in the exposure groups.

In the second experiment, 54 adult pregnant females, beginning on GD12, were exposed to 60 ppm AN for 4 h/d, 5 d/week for seven weeks and then 7 h/d, 5 d/week for 97 weeks. Gestation was permitted to proceed normally and the offspring (67 males and 54 females) were exposed on the same schedule as the dams. A statistically significant increase in the percentage of animals bearing malignant tumors and in the number of total malignant tumors per 100 animals was observed in female breeders and in male and female offspring exposed to AN. In addition, exposed offspring showed statistically significant increases in the incidence of malignant tumors

of the mammary gland and extrahepatic angiosarcomas in females; hepatomas and Zymbal's gland carcinomas in males; and encephalic gliomas in both male and female rats.

The AN Group (2013) indicated that the Maltoni et al. (1998) study has been the subject of recent pathology working group (PWG) peer review by NTP. The summary report of the NTP (2011) review stated that *"In general, there was good agreement between the Ramazzini Institute (RI) diagnosis and PWG opinions with some minor issues in terminology for neoplasms in the acrylonitrile".* The AN group further stated that while USEPA indicated their intention to consider results of the NTP peer review in a 2010 press release, because there were differences of opinion between NTP scientists and the Ramazzini Institute in the diagnoses of certain cancers conducted by the RI, USEPA IRIS chose to not use the Maltoni et al. (1988) tumor results to develop its inhalation unit risk for AN.

4.2.2.2 Epidemiological Studies

In humans, a number of epidemiological studies have been conducted to evaluate the association between tumors of the lung, brain, prostate and a variety of other organs and occupational exposure to AN. Several studies in the 1970s and 80s noted a link between occupational AN exposure and lung cancer, however, these findings have not been conclusively confirmed by larger, more recent studies. Many of the epidemiological studies suffer from deficiencies such as inadequate exposure assessment, short-term follow-up, small and relatively youthful cohorts, potential confounding factors by other occupational carcinogens and/or smoking, lack of consistently positive findings across studies and a lack of clear dose-response relationships for human cancer or lack of consideration of the effects of smoking (IARC 1999, IPCS 2002, Haber and Patterson 2005, NTP 2011). Overall, the epidemiology database does not suggest a relationship between AN exposure and cancers, including lung cancer (IARC 1999, Haber and Patterson 2005).

4.2.2.2.1 DuPont Studies

DuPont conducted the first epidemiological study addressing the potential carcinogenicity of AN. Several early epidemiological studies reported exposure levels and health effects in occupational cohorts at two DuPont chemical plants by O'Berg (1980 and 1985, as cited in USEPA 1991). O'Berg (1980) reported that workers' exposure to AN at a DuPont textile fiber plant developed lung cancer. However, the lung cancer incidence or mortality was not observed in a follow-up study of the same cohort five years later (O'Berg 1985), in a combined cohort study (Wood et al. 1998, as cited in IPCS 2002), a reevaluation of National Cancer Institute cohort study by Marsh et al. (2001), and an updated study of Wood et al. (1998) by Symons et al. (2008).

Symons et al. (2008) updated the prior DuPont studies by adding an additional 11 years of follow-up for mortality through 2002 to a cohort consisting of 2,548 male workers with at least six months of AN exposure between 1947 and 1991. There were 95,657 person-years of observation for the entire cohort and 23,368 for the AN exposed group. The exposed cohort was relatively large and the workers had some of the highest occupational AN exposures ever

reported. Over 67% of the cohort had mean intensity estimates of AN exposure greater than 2 ppm. Follow-up was complete for 99% of the cohort and there were a total of 839 deaths, 240 from all cancers. Most standardized mortality ratio (SMR) estimates are at or near no-effect levels. There were 88 lung cancer-related and 96 expected deaths (SMR=92; 95% CI: 75-114). Adjusted hazard ratio (HR) estimates indicate no increased mortality risk for lung cancer (HR= 0.95, 95% CI: 0.73-1.23). The highest lung cancer risk (HR=1.09, 95% CI: 0.67-1.77) occurred among the most heavily exposed subgroup of workers with a mean intensity of exposure of ≥ 10 ppm and a cumulative exposure of ≥ 10 ppm-years. The authors concluded that there is no evidence for increased cancer mortality among highly AN-exposed workers over five decades of follow-up.

Similar results were observed in other occupational epidemiology studies. In a review of the 18 published cohort studies, Sakurai (2000) concluded that there is no adequate evidence in humans for carcinogenicity for AN, however, the possibility of a causal association between the high AN concentration exposure and lung cancer in humans could not be excluded. The same conclusion was reached by other independent AN workers studies (Benn and Osborne 1998; Czeizel et al. 2004; and Swaen et al. 2004, as cited in IPCS 2002), meta-analysis (Sponsiello-Wang et al. 2006, Cole et al. 2008) and other reviews (ATSDR 1990, IARC 1999, Haber and Patterson 2005, AEGL 2007, Cole et al. 2008, NTP 2011). A recent review (Cole et al. 2008) identified 26 epidemiologic studies, which examined mortality and/or incidence rates among persons with AN exposure. This comprehensive review also concluded that information does not support an association of AN with any form of cancer in humans and that AN is not likely to cause lung cancer in humans.

4.2.2.2.2 Blair et al. (1998) Study

Blair et al. (1998) examined a large cohort of 25,460 workers (18,079 white men, 4,293 white women, 2,191 nonwhite men and 897 nonwhite women) originally assembled by the National Cancer Institute (NCI) from eight AN producing and using facilities in the U.S. The study attempted to adjust for known problems with earlier studies by quantifying exposures, estimating the effect of smoking and using an internal control group of unexposed workers. Mortality rates between the AN exposed and unexposed workers were compared using Poisson regression. The results indicated that there was no association between AN exposure and stomach, brain, breast, prostate or lymphatic cancer due to the small number of site-specific cancer deaths. The AN-exposed cohort as a whole experienced fewer deaths from lung cancer than those expected from the experience of the general U.S. population, but when the exposed workers were grouped into five quintiles of cumulative exposure, the lung cancer rate in the highest quintile of exposure (> 8 ppm-years) who were followed for ≥ 20 years was about two times the rate in the unexposed group of workers (relative risk (RR) = 2.1; 95% CI = 1.2–3.8). The excess of lung cancer in the highest quintile of cumulative exposure may indicate carcinogenic activity at the highest levels of AN exposure. However, analyses of exposure-response did not provide strong or consistent evidence for a causal association. The authors concluded that high levels of AN exposure are necessary before lung cancer risks are increased, or could be due to confounding, exposure misclassification, or chance.

4.2.2.3 Carcinogenic MOA

The MOA for AN-induced tumors in the lung, liver, Zymbal's gland, mammary gland, intestine and tongue have received little or no investigation. Kirman et al. (2005) indicated that AN and its stable metabolites, CEO and CN^{-1}, are capable of crossing the blood-brain barrier; and a possible MOA whereby AN produces brain tumors in rats may involve direct genotoxicity, indirect genotoxicity (oxidative stress) and non-genotoxic mechanisms. However, data supporting a non-genotoxic MOA are limited to a single *in vitro* study. CEO is a direct-acting mutagen which binds DNA with a much greater affinity than AN (Woutersen 1998). The hypothesized MOA involves mutagenesis n by CEO. CEO is thought to be distributed to target organs (e.g., rat brain) where it reacts with DNA, forming DNA adducts that lead to mutations and initiate tumor formation. Other types of DNA damage by CEO are also observed *in vivo* such as DNA strand breaks, sister chromatid exchanges and micronucleus formation. However, an independent peer review panel conducted by the Toxicology Excellence for Risk Assessment (Haber and Patterson, 2005) indicated that an overall WOE evaluation does not support direct DNA reactivity as a predominant contributor to AN carcinogenesis in rodents.

Other MOAs, including oxidative stress and inhibition of intercellular communication, may also contribute. IARC (1999) indicates that toxicity might lead to tumor formation by an indirect mechanism. Kirman et al. (2005) indicated that since no measurable DNA adducts were observed in rat brain, the genotoxic MOA is not likely for AN in producing rat brain tumors. Kirman et al. (2005) further indicated that the WOE supports that rat brain tumors are likely the result of an epigenetic MOA involving oxidative stress. Whysner et al. (1996), as cited in Woutersen (1998), reported that formation of 8-oxodeoxyguanosine in brain DNA, reflecting oxidative tissue damage, was observed in rats exposed to AN. The findings may indicate an epigenetic, rather than mutagenic mechanism involved in the induction of tumors in the brain of rats exposed to AN (Woutersen 1998). AN is toxic in rats at high concentrations, which is possibly related to GSH-depleting activity. However, such GSH-depleting activity will probably not occur at low-level human exposure because humans may possess an additional detoxification pathway for CEO by epoxide hydrolase, which should decrease the amount of CEO leaving the liver for the systemic circulation, relative to rats, where this pathway is not operative (EU 2004).

4.2.2.4 WOE Classifications

AN was classified by IARC (1999) as Group 2B (possibly carcinogenic to humans), based on insufficient evidence in humans and sufficient evidence in experimental animals. NTP (2011) classifies AN as "reasonably anticipated to be a human carcinogen." However, this was based solely on sufficient evidence in experimental animals, as the epidemiologic data were considered "inadequate" to support carcinogenicity in humans.

4.2.2.5 Conclusions

In summary, AN is an animal carcinogen at high doses, however, there is a lack of association with exposure to AN and cancer in humans from several large cohort studies. Available epidemiologic studies do not demonstrate a significant dose-response relationship between AN

exposure and human cancer risk. These studies conclude that AN is not likely to cause cancer in humans at exposure levels encountered in the environment, although some epidemiological studies indicate a possible association between occupational exposure to AN at high levels (e.g., orders of magnitude higher than environmental exposure) and increased risk of lung cancer (NTP 2011). The overall carcinogenic WOE shows that while AN is capable of causing tumors in rats and mice at high doses, AN does not appear to contribute to the development of cancerous tumors in humans. Therefore, TCEQ concludes that AN is not likely to be human carcinogen. According to TCEQ guidelines, the TCEQ only performs carcinogenic dose-response assessments for chemicals considered "Carcinogenic to Humans" and "Likely to Be Carcinogenic to Humans" (TCEQ 2012). Therefore, based on the aforementioned WOE, the TCEQ determined not to derive the $^{chronic}ESL_{threshold(c)}$. This is consistent with the NCSAB (2010) decision not to propose a cancer-based AAL for AN in its 2010 Toxicity Assessment.

4.2.3 Comparison of TCEQ $^{chronic}ESL_{threshold(nc)}$ and Estimated URF Values Derived by USEPA (1991)

USEPA (1991) estimated an inhalation unit risk (IUR) (or URF) of 6.8×10^{-5} per µg/m^3 for AN. The IUR was based on the excess incidence of respiratory cancer in the O'Berg (1980) study adjusted for smoking. The IUR was calculated from a relative risk model and based on a continuous lifetime equivalent of occupational exposure (an exposure concentration of 15 ppm was assumed to be the 8-h TWA with average exposure duration of 9 years).

While no URF is derived by TCEQ, the derived $^{chronic}ESL_{threshold(nc)}$ of 0.7 µg/m^3 is within the range of the concentrations at 1×10^{-5} cancer risk estimated by USEPA (1991). The derived $^{chronic}ESL_{threshold(nc)}$ is expected to be protective against any potential cancer risk, though the TCEQ considers this risk to be minimal.

4.3 Welfare-Based Chronic ESL

No information was found to indicate that chronic vegetation effects result from exposure to AN.

4.4 Chronic ESL and Values for Air Monitoring Evaluation

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

Chronic ReV = 7.1 µg/m^3 (3.3 ppb)
$^{chronic}ESL_{threshold(nc)}$ = 2.1 µg/m^3 (1 ppb)

The long-term ESL for air permit evaluations is the $^{chronic}ESL_{threshold(nc)}$ of 2.1 µg/m^3 (1 ppb) as no $^{chronic}ESL_{nonthreshold(c)}$ was derived (Table 2). The $^{chronic}ESL_{threshold(nc)}$ is set to protect against noncancerous nasal lesions resulting from chronic exposure.

4.5 Chronic Inhalation Observed Adverse Effect Level

The BMC_{10} value of 1.533 ppm from the female rat model from Quast et al. (1980) (Table 9) was used as the initial POD for calculation of a chronic inhalation observed adverse effect level.

No duration adjustment was made (TCEQ 2012). However, an animal-to-human dosimetric adjustment was made to the BMC_{10} to calculate a $BMC_{10\ HEC}$:

For Category 1 gases, the $BMC_{10\ HEC}$ was calculated using the following equation:

$BMC_{10HEC} = BMC_{10} \times RGDR_{ET}$ (Section 4.1.6.2.1)
= 1.533 ppm x 1
= 1.533 ppm
= 1,500 ppb (rounded to two significant figures)

The BMC_{10HEC} determined from animal studies, where possible effects occurred in some 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 key study (or longer durations). Importantly, effects are not a certainty due to potential interspecies and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 1,500 ppb is provided for informational purposes only (TCEQ 2012).

The margin of exposure between the chronic inhalation observed adverse effect level of 1,500 ppb to the ReV of 3.3 ppb is a factor of 450.

Chapter 5. References

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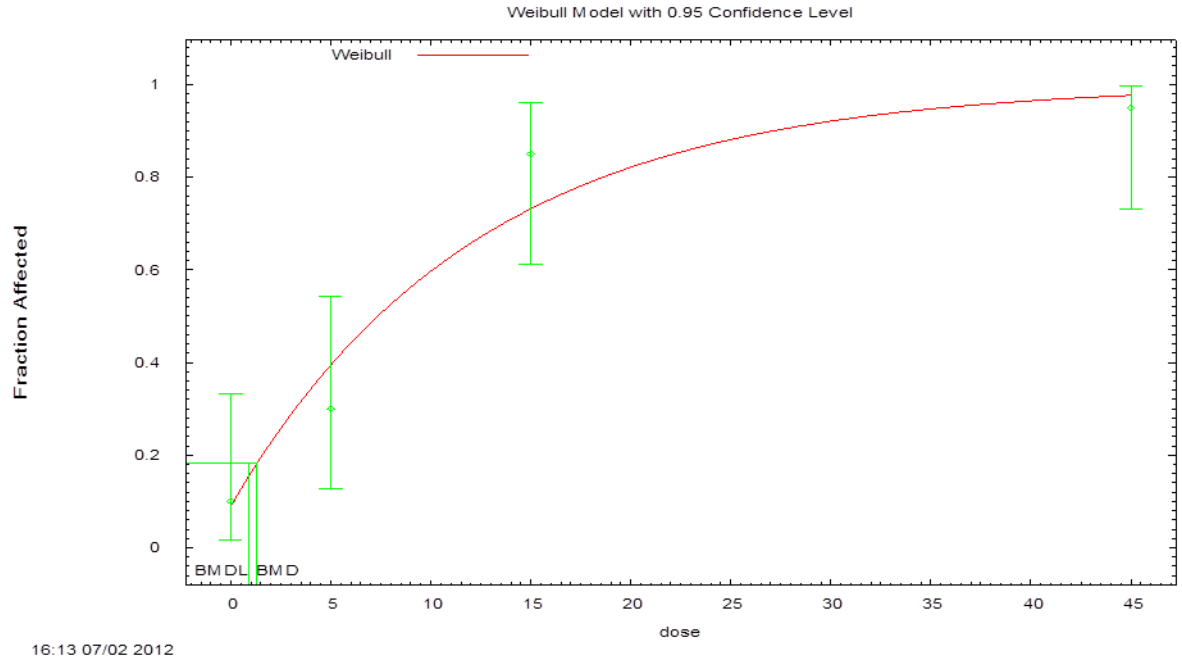
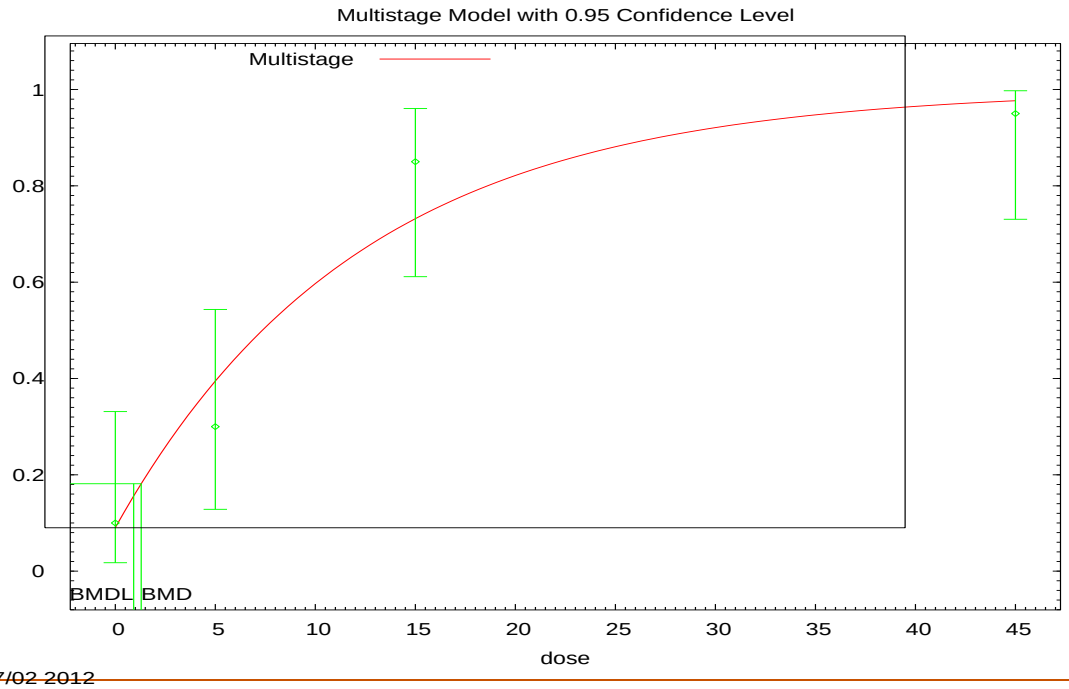
Appendix A. BMC Modeling (Nemec et al. 2008)

Table A 1 Summary of BMC Modeling Results for Hyperplasia in Respiratory/Transitional Epithelium in F1 Male and Female Rats

Dichotomous Model	AIC	P-value	Scaled residuals	BMC_{10}	$BMCL_{10}$
Gamma Multi-Hit	71.13	0.0875	< |2|	1.52	0.921
Logistic	73.15	0.0005	< |2|	3.048	2.20
Log-Logistic	69.12	0.3394	< |2|	2.872	1.105
LogProbit	69.67	0.2279	< |2|	2.733	1.019
Multistage	69.17	0.2443	< |2|	1.295	0.919
Probit	75.84	0.0031	< |2|	3.408	2.535
Weibull	69.16	0.2443	< |2|	1.295	0.919
Quantal	69.16	0.2443	< |2|	1.295	0.919




Multistage Model with 0.95 Confidence Level
Multistage
1
0.8
0.6
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BMDL BMD
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5
10
15
20
25
30
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dose
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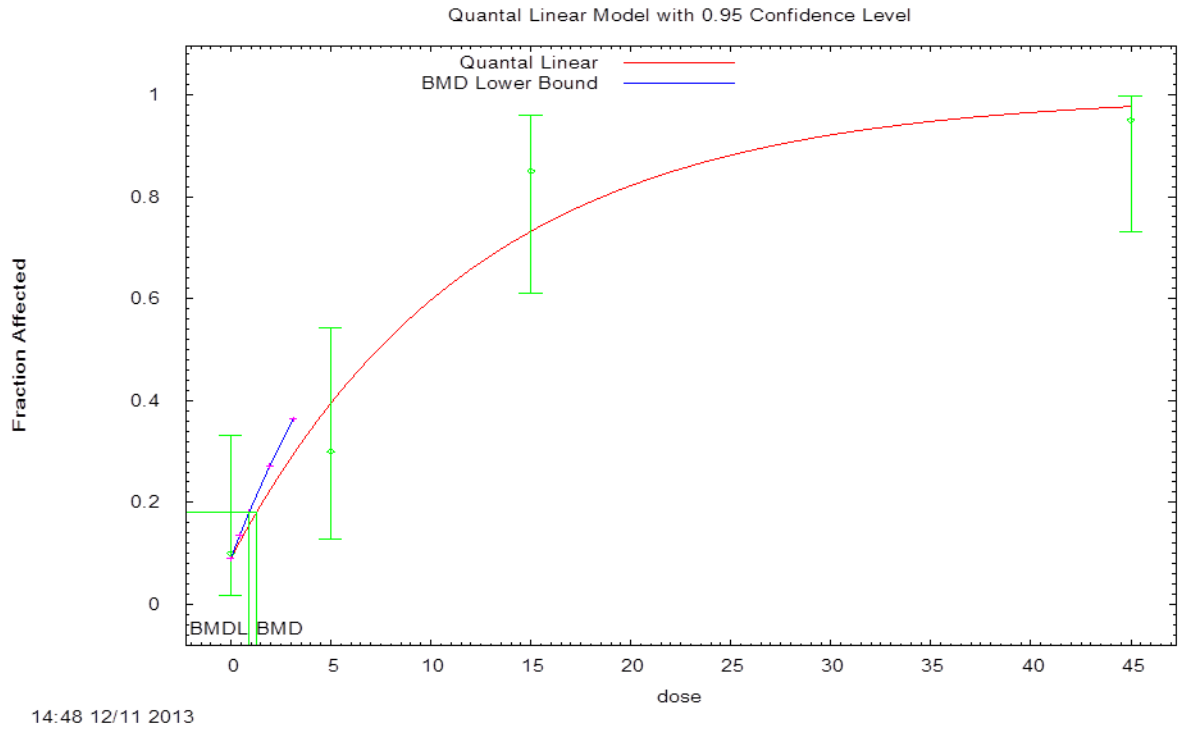
Quantal Linear Model with 0.95 Confidence Level
Quantal Linear
BMD Lower Bound
Fraction Affected
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0.8
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BMDL BMD
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20
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45
dose
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Appendix B. BMC Modeling Noncancer (Quast et al. 1980)

Table B 1 Summary of BMC Modeling Results Based on Incidence of Hyperplasia of Mucus-Secreting Cells in Male Rats

Dichotomous Model	AIC	P-value	Scaled residuals	BMC_{10}	$BMDC_{10}$
Gamma Multi-Hit	30.22	0.3499	< |2|	3.739	2.383
Logistic	37.99	0.0156	< |2|	11.01	6.781
LogProbit	30.31	1.000	< |2|	0.755	Failed
Log-Logistic	28.42	0.9429	< |2|	1.778	0.777
Probit	37.94	0.0152	< |2|	11.02	7.320
Multistage	30.22	0.3499	< |2|	3.739	2.383
Weibull	30.22	0.3499	< |2|	3.739	2.383
Quantal	30.22	0.3499	< |2|	3.739	2.383

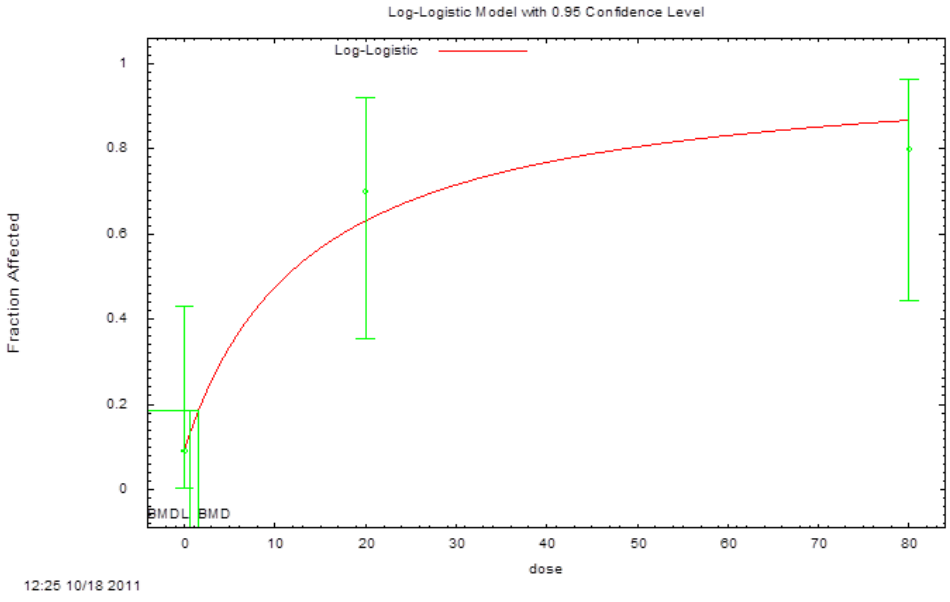

Table B 2 Summary of BMC Modeling Results Based on Incidence of Hyperplasia in the Nasal Turbinates in Male Rats

Dichotomous Model	AIC	P-value	Scaled residuals	BMC_{10}	$BMCL_{10}$
Gamma Multi-Hit	19.28	0.997	< |2|	15.345	2.961
Logistic	19.28	0.998	< |2|	18.337	7.547
LogProbit	19.28	0.998	< |2|	17.941	6.284
Log-Logistic	19.28	0.998	< |2|	16.494	6.178
Multistage	17.30	0.9925	< |2|	10.084	2.789
Probit	19.28	0.998	< |2|	16.763	6.878
Weibull	19.28	0.994	< |2|	12.134	2.961
Quantal	19.84	0.4172	< |2|	3.332	2.007

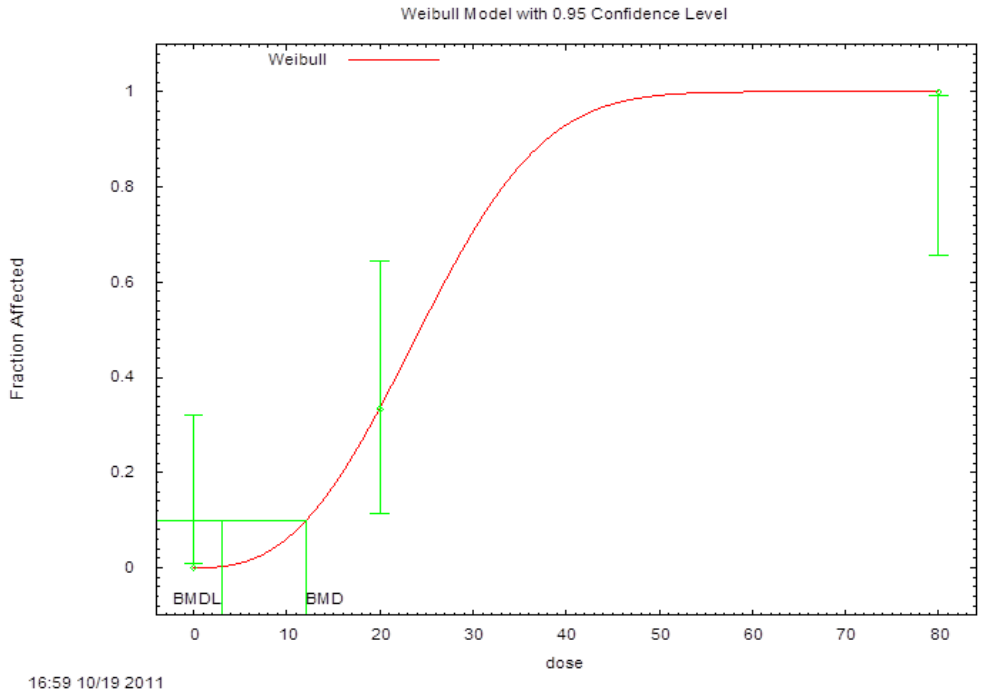

Table B 3 Summary of BMC Modeling Results Based on Incidence of Focal Inflammation in the Nasal Turbinates in Female Rats

Dichotomous Model	AIC	P-value	Scaled residuals	BMC_{10}	$BMCL_{10}$
Gamma Multi-Hit	41.66	0.2106	< |2|	7.048	3.607
Logistic	42.48	0.1275	< |2|	13.06	7.656
Log-Logistic	40.75	0.4185	< |2|	3.472	1.247
LogProbit	42.11	NA	< |2|	0.06	Failed
Multistage	41.66	0.2106	< |2|	7.048	3.607
Probit	42.48	0.1275	< |2|	13.04	8.066
Weibull	41.66	0.2106	< |2|	7.048	3.607
Quantal	41.66	0.2106	< |2|	7.048	3.607

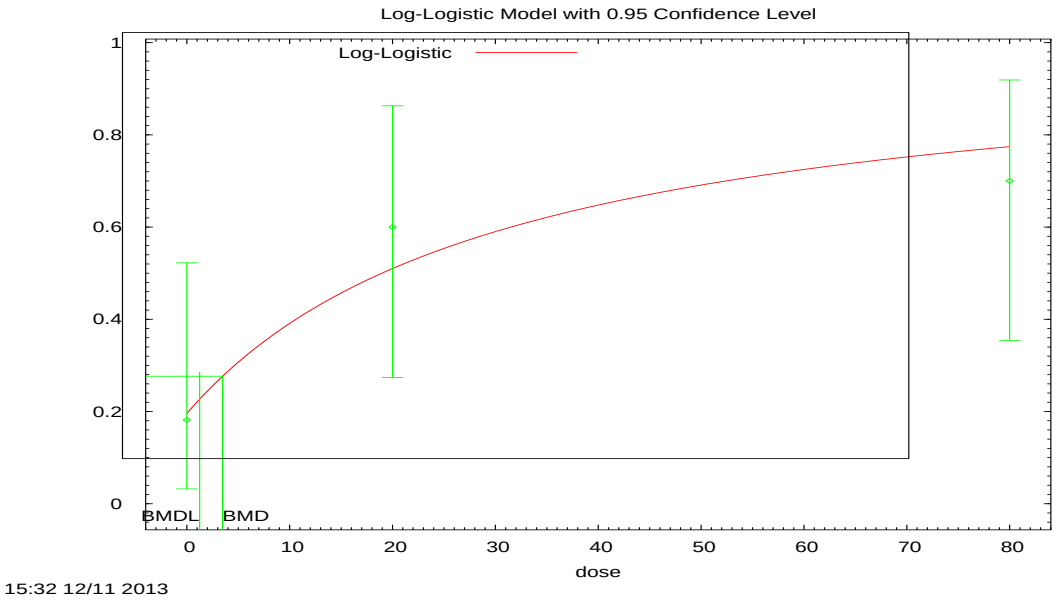

Table B 4 Summary of BMC Modeling Results Based on Incidence of Flattening of the Nasal Turbinates in Female Rats

Dichotomous Model	AIC	P-value	Scaled residuals	BMC_{10}	$BMCL_{10}$
Gamma Multi-Hit	35.73	0.0866	< |2|	3.951	2.316
Logistic	38.43	0.0238	< |2|	9.585	5.748
Log-Logistic	33.49	0.4401	< |2|	1.533	0.564
LogProbit	34.93	NA	< |2|	0.015	Failed
Multistage	35.73	0.0866	< |2|	3.951	2.316
Probit	38.49	0.023	< |2|	9.859	6.431
Weibull	35.73	0.0866	< |2|	3.951	2.316
Quantal	35.73	0.0866	< |2|	3.951	2.316