Development Support Document
Final, August 7, 2008
Accessible 2013
24-Hour Reference Value added, September 14, 2015

Formaldehyde

CAS Registry Number: 50-00-0

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Revision History

Original Development Support Document (DSD) posted as final on August 7, 2008.

Revised DSD September 14, 2015: the 24 hour reference value (ReV) was added to the Summary Tables and the derivation of the 24-hour ReV was added as Appendix E. Refer to TCEQ (2015) for guidelines on deriving 24-hour ReVs. Two minor corrections to: 1) odor value rounding, and 2) molecular weight.

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Chapter 1 Summary Tables

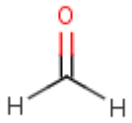
Table 1 provides a summary of health- and welfare-based values resulting from an acute and chronic evaluation of formaldehyde. Table 2 provides summary information on formaldehyde's physical/chemical data.

Table 1 Health- and Welfare-Based Values

Short-Term Values	**Concentration**	**Notes**
$^{acute}ESL$ [1 h] (HQ = 0.3)	15 µg/m^3 (12 ppb) **Short-Term ESL for Air Permit Reviews**	**Critical Effect(s):** eye and nose irritation in human volunteers
acute ReV [1 h] (HQ = 1.0)	50 µg/m^3 (41 ppb)*	**Critical Effect(s):** Same as above
acute ReV [24 h] (HQ =1)	50 µg/m^3 (41 ppb) [a, b]	**Critical Effect(s):** Same as above
$^{acute}ESL_{odor}$	610 µg/m^3 (500 ppb) [a]	50% odor detection threshold; pungent, highly irritating odor
$^{acute}ESL_{veg}$	---	concentrations producing vegetative effects were significantly above other ESLs
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	3.3 µg/m^3 (2.7 ppb) **Long-Term ESL for Air Permit Reviews**	**Critical Effect**: elevated rates of symptoms such as eye, nasal, and lower airway discomfort in humans
chronic ReV (noncarcinogenic) (HQ = 1.0)	11 µg/m^3 (8.9 ppb) [a]	**Critical Effect(s):** Same as above
$^{chronic}ESL_{nonlinear(c)}$ (HQ = 0.3)	5.5 µg/m^3 (4.5 ppb)	**Cancer Endpoint:** nasopharyngeal cancer
chronic ReV (carcinogenic/nonlinear) (HQ = 1.0)	18 µg/m^3 (15 ppb) [a]	**Critical Effect:** cell proliferation/cytotoxicity in rats
$^{chronic}ESL_{veg}$	---	concentrations producing vegetative effects were significantly above other ESLs

[a] Values that may be used for evaluation of ambient air monitoring data.
[b] Appendix E provides the derivation of the 24 hour ReV for formaldehyde
Abbreviations used: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; **h**, hour; **HQ**, hazard quotient; **ESL**, Effects Screening Level; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{nonlinear(c)}$**, chronic health-based ESL for nonlinear dose-response cancer effects; **$^{chronic}ESL_{nonlinear(nc)}$**, chronic health-based ESL for nonlinear dose-response noncancer effects; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

Table 2 Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	CH_2O	ATSDR (1999)
Chemical Structure		ChemIDplus
Molecular Weight	30.03 (g/mole)	TRRP (2006)
Physical State	gas	ATSDR (1999)
Color	colorless	ATSDR (1999)
Odor	pungent, suffocating, highly irritating odor	ATSDR (1999)
CAS Registry Number	50-00-0	TRRP (2006)
Synonyms and Trade Names	Synonyms: formic aldehyde, methanal, methyl aldehyde, methylene oxide Trade Names: aqueous - Formalin, Formol, Morbicid, Veracur; polymeric form - Paraformaldehyde, Polyoxymethylene, Paraform, Formagene [1]; Synonyms/Trade Names: aldehyde formique (French), aldehyd mravenci (Czech), aldeide formica (Italian), BFV, FA, foraldehyd (Czech, Polish), formalith, fyde, hoch, ivalon, karsan, lysoform, methlene glycol, NCI-C02799, oplossingen (Dutch), oxomethane, oxymethylene, polyoxymethylene glycols, RCRA Waste U122, superlysoform, UN 1198 or 2209 (DOT) [2]	[1] ATSDR (1999) [2] IRIS (1989)
Solubility in water	550,000 mg/L	TRRP (2006)
Low K_{ow}	0.35	TRRP (2006)
Vapor Pressure	3,880 mm Hg at 25°C	TRRP (2006)
Vapor Density (air = 1)	.1.0 g/L at 0° C and 1 atm	NAS (1995)
Density (water = 1)	0.815 g/ml at -20° C	ATSDR (1999)
Melting Point	-92° C	ATSDR (1999)
Boiling Point	-21° C	ATSDR (1999)
Conversion Factors	1 µg/m^3 = 0.813 ppb @ 25°C 1 ppb = 1.23 µg/m^3	ATSDR (1999)

Chapter 2 Major Sources and Use

2.1 Sources

General information on formaldehyde sources, taken from the Agency for Toxic Substances and Disease Registry (ATSDR 1999), is given below.

> Formaldehyde is produced by both anthropogenic and natural sources. Combustion processes account directly or indirectly for most of the formaldehyde entering the environment. Direct combustion sources include power plants, incinerators, refineries, wood stoves, kerosene heaters, and cigarettes. Formaldehyde is produced indirectly by photochemical oxidation of hydrocarbons or other formaldehyde precursors that are released from combustion processes (NRC 1981). During smog episodes, indirect production of formaldehyde may be greater than direct emissions (Fishbein 1992). Oxidation of methane is the dominant source of formaldehyde in regions remote from hydrocarbon emissions (Staffelbach et al. 1991). Other anthropogenic sources of formaldehyde in the environment include vent gas from formaldehyde production; exhaust from diesel and gasoline-powered motor vehicles; emissions from the use of formaldehyde as a fumigant, soil disinfectant, embalming fluid, and leather tanning agent; emissions from resins in particle board, and plywood; emissions from resin-treated fabrics and paper; waste water from the production and use of formaldehyde in the manufacture of various resins and as a chemical intermediate; and waste water from the use of formaldehyde-containing resins (EPA 1976a; Kleindienst et al. 1986; NRC 1981; Verschueren 1983). Natural sources of formaldehyde include forest fires, animal wastes, microbial products of biological systems, and plant volatiles.
>
> Formaldehyde is naturally produced in very small amounts in our bodies as a part of our normal, everyday metabolism and causes us no harm. It can also be found in the air that we breathe at home and at work, in the food we eat, and in some products that we put on our skin. A major source of formaldehyde that we breathe every day is found in smog in the lower atmosphere. Automobile exhaust from cars without catalytic converters or those using oxygenated gasoline also contain formaldehyde. At home, formaldehyde is produced by cigarettes and other tobacco products, gas cookers, and open fireplaces.
>
> The input of formaldehyde into the environment is counterbalanced by its removal by several pathways. Formaldehyde is removed from the air by direct photolysis and oxidation by photochemically produced hydroxyl and nitrate radicals. Measured or estimated half-lives for formaldehyde in the atmosphere range from 1.6 to 19 hours, depending upon estimates of radiant energy, the presence and concentrations of other pollutants, and other factors (Atkinson and Pitts 1978; DOT 1980; EPA 1982; Lowe et al. 1980; Su et al. 1979).

Under clear daytime conditions, estimated residence time in the air may be on the higher end of the above-referenced range and is determined primarily by reaction with the hydroxyl (OH) radical. Under rainy nighttime conditions, residence time may be on the lower end of the range due to wet deposition (Chenier 2003). See Section 5.2 of ATSDR (1999) for additional source information.

As mentioned above, formaldehyde is produced endogenously in our bodies. Normal levels exhaled in human breath have been reported to be significant (Moser et al. 2005), although TS has serious concerns about the analytical method used. However, exogenous sources are also important. The United States Environmental Protection Agency's (USEPA) 2001 National-Scale Air Toxics Assessment (NATA) of emissions from the 1996 National Toxics Inventory (NTI) indicated that statewide, formaldehyde emissions from mobile sources (onroad and nonroad) accounted for approximately 56.5% of the NTI formaldehyde emissions in Texas, with major facility sources and area/other sources (e.g., smaller facilities) comprising the remainder (USEPA 2001).

The levels of formaldehyde in indoor air are often ten times higher (or more) than levels outdoors, depending on many factors (e.g., ventilation, indoor sources such as pressed wood products, carpets, paints, cooking) (IARC 2006b). For example, average residential indoor air concentrations in Canada are perhaps an order of magnitude higher than outdoor air concentrations, with a reported average of 29.2 ppb indoors versus 2.7 ppb outdoors (Liteplo and Meek 2003). In a 1997 European study (Jurvelin et al. 2003), the mean indoor residential level was 33.3 ppb compared to the mean outdoor residential level of 2.6 ppb, with the mean personal exposure concentration reported as 21.4 ppb (IARC 2006b). In US residential indoor air, reported mean levels range from approximately 10-374 ppb, including manufactured houses, with the majority of reported means falling below 40 ppb (see Table 14 of IARC 2006b). Other studies have reported average indoor household concentrations of 26-30 ppb (mean of 26 ppb in Krzyzanowski et al. 1990, 30 ppb in USEPA 1984 as cited in Imbus 1985, 28.5 ppb in Quackenboss et al. 1989). Mobile homes may have mean air formaldehyde levels of several hundred ppb (380-900 ppb), with peak concentrations potentially up to several thousand ppb (1,770-4,200 ppb) (Gough et al. 1984, NAS/NRC 1980, ATSDR 2007) and higher concentrations in newer homes (Garry et al. 1980). In US office building indoor air, the range of geometric mean concentrations reported for one study (Reynolds et al. 2001) was approximately 1.4-10.8 ppb, and the median in another study (Shah and Singh 1988) was reported to be 65 ppb (see Table 12 of IARC 2006b). New York and Los Angeles high school students have been reported to have similar personal (≈ 22 ppb), indoor home (≈ 18 ppb), and outdoor (≈ 4 ppb) exposure levels (Sax et al. 2006).

2.2 Uses

Formaldehyde is produced on a large scale and is used mainly in the production of phenolic, urea, melamine, and polyacetal resins. These resins are used widely as adhesives and binders in wood products, pulp and paper, synthetic vitreous fiber industries, textile finishing, and the production of plastics and coatings. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals (e.g., 1,4-butanediol), and in aqueous solution (formalin) as a disinfectant and preservative. Historically, the highest occupational exposure levels (approximately 2-5 ppm) have been measured in the varnishing of furniture and wooden floors, finishing of textiles, garment industry, treatment of fur, in manufactured board mills and foundries, and for embalmers, pathologists, and paper workers (IARC 2006a).

Additional information on formaldehyde uses, taken from ATSDR (1999), is given below.

Formaldehyde is used in many industries. It is used in the production of fertilizer, paper,

> plywood, and urea-formaldehyde resins. It is present in the air in iron foundries. It is also used in the production of cosmetics and sugar, in well-drilling fluids, in agriculture as a preservative for grains and seed dressings, in the rubber industry in the production of latex, in leather tanning, in wood preservation, and in photographic film production. Formaldehyde is combined with methanol and buffers to make embalming fluid. Formaldehyde is also used in many hospitals and laboratories to preserve tissue specimens…It is also used as a preservative in some foods, such as some types of Italian cheeses, dried foods, and fish. Formaldehyde is found in many products used every day around the house, such as antiseptics, medicines, cosmetics, dish-washing liquids, fabric softeners, shoe-care agents, carpet cleaners, glues and adhesives, lacquers, paper, plastics, and some types of wood products. Some people are exposed to higher levels of formaldehyde if they live in a new mobile home, as formaldehyde is given off as a gas from the manufactured wood products used in these homes.

See Section 4.3 of ATSDR (1999) for additional use information.

Chapter 3 Acute Evaluation

3.1 Health-Based Acute ReV and ESL

3.1.1 Physical/Chemical Properties and Key Studies

3.1.1.1 Physical/Chemical Properties

Formaldehyde is a colorless, flammable gas at room temperature and has a pungent, distinct odor (ATSDR 1999). The main chemical and physical properties of formaldehyde are summarized in Table 2. Due to being highly water soluble and reactive, inhalation exposure to formaldehyde produces mainly point-of-entry (POE) effects and is treated as a Category 1 Gas (USEPA 1994).

3.1.1.2 Essential Data and Key Studies

Both human and animal noncarcinogenic studies indicate that the critical target organs for airborne formaldehyde are the nose and eyes, with the lungs being a secondary target at much higher concentrations (ATSDR 1999). In other words, in both human studies (e.g., acute, occupational, residential) and animal studies (i.e., acute, intermediate, chronic), the most sensitive or critical endpoint for exposure to formaldehyde is irritation of the eyes and upper respiratory tract (i.e., nasopharyx, oral cavity, and throat), nose and throat irritation more specifically, with the eye generally being most sensitive (ATSDR 1999, Noisel et al. 2007). At concentrations higher than those generally associated with sensory irritation, small reversible effects on lung function have occurred (Liteplo and Meek 2003). Tissues and organs distant from the portal-of-entry do not experience toxic effects from formaldehyde levels normally expected in ambient and workplace air due to rapid, detoxifying metabolism. Additionally, results from animal toxicity, pharmacokinetic, and anatomical airflow studies indicate that formaldehyde does not reach lower regions of the respiratory tract at exposure concentrations ≤ 1 ppm (ATSDR 1999).

3.1.1.2.1 Human Studies

Human inhalation studies on the short-term (i.e., acute) irritant effects of formaldehyde are available and preferred over animal studies for the calculation of an acute Reference Value (ReV) and acute Effects Screening Level (^{acute}ESL). A summary of human and animal studies may be found in ATSDR (1999).

Irritation of the eyes, nose, and throat are well-documented effects of acute, low-concentration exposure to formaldehyde. The irritant effects of formaldehyde are restricted to portal-of-entry tissues due to the high water solubility and reactivity of formaldehyde, as well as the ability of cells to rapidly metabolize and detoxify formaldehyde. Studies of humans under controlled conditions clearly indicate that acute (short-term) exposures to air concentrations ranging from 0.4 to 3 ppm induce reversible mild to moderate eye, nose, and throat irritation, produce changes in nasal lavage fluid contents indicative of irritation of the nasal epithelium, and do not consistently or markedly affect pulmonary function variables in most individuals (ATSDR 1999). Controlled human exposure studies provide the best dose-response data on the irritancy of formaldehyde for quantitative risk assessment (NAS/NRC 1980). Two such studies, Pazdrak et al. (1993) and Krakowiak et al. (1998), are used as key studies for derivation of the acute ReV and ^{acute}ESL.

Key Studies - Pazdrak et al. (1993)

Pazdrak et al. (1993) exposed 20 volunteers, nine of whom had skin hypersensitivity to formaldehyde, to 0.5 mg/m^3 (0.4 ppm) formaldehyde for 2 h. Clean air served as placebo. Symptoms of rhinitis (i.e., number of sneezes, degree of mucosal edema, rhinorrhea, itching) were measured and scored. Nasal lavage was performed before exposure, immediately after, and 4 and 18 h after exposure had ended. Morphological (e.g., cell number, differential count) and biochemical (e.g., albumin and total protein levels) changes in nasal lavage fluid were evaluated. The total number of eosinophils and basophils (metachromatic cells) were determined, and the differential count determined number of epithelial cells, eosinophils, neutrophils, basophils, and mononuclear cells (includes lymphocytes and monocytes) per 200 cells. The study showed transient burning sensation of the eyes and nasal passages, transient symptoms of rhinitis (i.e., increased itching, sneezing, and congestion), and nasal washing changes (i.e., increased eosinophil count/proportion, albumin, and total protein levels) at 0.5 mg/m^3 (0.4 ppm). Tryptase concentration in nasal lavage was also measured but did not show any increase. Tryptase is involved in the allergic response, the most abundant secretory granule-derived serine protease contained in mast cells, and a measure of mast cell degranulation. The study authors concluded that the lack of evidence for mast cell degranulation (release of inflammation mediators such as histamine), the unchanged number of basophils, and the similarity of responses in healthy and sensitized subjects indicate the occurrence of nonspecific, nonallergic inflammatory processes in the nasal mucosa. *The lowest-observed-adverse-effect level (LOAEL) from Pazdrak et al. (1993) is 0.5 mg/m^3 (0.4 ppm) based on transient burning sensation of the eyes and nasal passages and transient symptoms of rhinitis.* Pazdrak et al. (1993) was used by ATSDR (1999) in derivation of the acute inhalation minimal risk level (MRL).

Key Studies - Krakowiak et al. (1998)

Krakowiak et al. (1998) exposed 20 volunteers to 0.5 mg/m^3 (0.4 ppm) formaldehyde for 2 h. Ten of the volunteers had occupational exposure to formaldehyde, had historically experienced

rhinitis and asthmatic symptoms in the workplace, were suspected of having respiratory formaldehyde sensitization, and had been diagnosed with bronchial asthma probably being due to formaldehyde exposure (i.e., formaldehyde-induced asthma). Clean air served as placebo. Nasal symptoms (i.e., number of sneezes, degree of mucosal edema, rhinorrhea, itching) were measured and scored. The occurrence and intensity of clinical symptoms from the lower respiratory tract (i.e., coughing, dyspnea (shortness of breath)) were also recorded. Nasal lavage was performed before exposure, immediately after, and 4 and 24 h after exposure had ended. Morphological changes in nasal lavage fluid were evaluated. The total number of eosinophils and basophils (metachromatic cells) were determined, and the differential count determined number of epithelial cells, eosinophils, basophils, and mononuclear cells (includes lymphocytes and monocytes) per 200 cells. Biochemical (e.g., albumin, total protein, tryptase, and eosinophil cationic protein levels) changes in nasal lavage fluid were also evaluated. Bronchial response was measured by spirometry. Forced expiratory volume in 1 second (FEV_1) was measured prior to exposure, immediately after, and 5 and 24 h after exposure. Peak expiratory flow (PEF) was measured at the beginning of exposure and every hour for 12 h, and again at 24 h after exposure. A histamine inhalation test utilizing various concentrations (0.03, 0.06, 0.125, 0.250, 0.5, 1, 2, 4, 8, and 16 mg/ml) and FEV_1 measurements was performed at the beginning of exposure, 5 minutes into the exposure, and 24 h after exposure. $PC_{20}H$ was defined as the histamine dose producing a twenty percent decrease in FEV_1. Total serum immunoglobulin gamma E (IgE) and formaldehyde-specific serum IgE antibodies were measured.

The 0.4 ppm exposure in Krakowiak et al. (1998) produced transient symptoms of rhinitis (i.e., increased sneezing, itching, and congestion) in all subjects, which were most severe immediately after inhalation (less severe 4 h later). There was no significant difference in nasal response between healthy subjects and asthmatic subjects occupationally exposed to formaldehyde. A typical allergen challenge triggers both the influx of mast cells and eosinophils (leukocytes which play major roles in allergic and inflammatory responses), and the pronounced increase in the concentrations of their respective enzymes, tryptase and eosinophil cationic protein. Combined, these may be used as markers of nasal allergic reaction. The number of eosinophils and leukocytes increased following exposure, while the levels of tryptase and eosinophil cationic protein did not. Regarding pulmonary function, no asthmatic subjects developed clinical symptoms of bronchial irritation, and there were no significant changes in FEV_1, PEF, or $PC_{20}H$ values in healthy or asthmatic subjects due to formaldehyde exposure, although the baseline FEV_1 and PEF values for healthy and asthmatic subjects differed. Formaldehyde did not increase the bronchial response to histamine ($PC_{20}H$) in asthmatic subjects. No formaldehyde-specific IgE antibodies were detected in asthmatic subjects with occupational exposure. The authors concluded that the lack of evidence for mast cell and eosinophil degranulation and the similarity of responses in healthy and asthmatic subjects indicate the occurrence of nonspecific, nonallergic inflammatory processes in the nasal mucosa. *The LOAEL from Krakowiak et al. (1998) is 0.5 mg/m^3 (0.4 ppm) based on transient symptoms of rhinitis.*

Supporting Study - Kulle et al. (1987, 1993)

Pazdrak et al. (1993) and Krakowiak et al. (1998) are supported by Kulle et al. (1987, 1993), which had a no-observed-adverse-effect-level (NOAEL) for eye irritation (0.5 ppm) higher than the LOAELs from the two key studies (0.4 ppm). Kulle et al. (1987, 1993) examined pulmonary function and irritant symptoms in 19 volunteers exposed to up to 3 ppm at rest (plus 2 ppm when

exercising) for 3 h. Exposure groups included formaldehyde concentrations of 0, 0.5, 1.0, 2.0, and 3.0 ppm. There were no significant decreases in pulmonary function or increases in bronchial reactivity in response to methacholine. Exercise significantly increased nose/throat irritation. Nasal flow resistance was increased at 3.0 ppm. Significant dose-response relationships in odor and eye irritation were observed. Mild eye irritation (21% of subjects) and moderate eye irritation (5% of subjects) were observed at 1 ppm but not 0.5 ppm. Kulle (1993) reexamined the response data with additional statistical methodology and estimated threshold levels as 0.5 to 1.0 ppm for eye irritation and 1.0 ppm for nose/throat irritation. *The LOAEL and NOAEL based on eye irritation in Kulle et al. (1987, 1993) are 1 ppm and 0.5 ppm, respectively.*

Data from Kulle et al. (1993) are amenable to BMD modeling. Therefore, the Toxicology Section (TS) of TCEQ performed BMD modeling on the eye irritation data (i.e., mild, moderate, mild/moderate combined) presented in Table 3 of Kulle et al. (1993) using USEPA BMD Modeling Software Version 1.4.1. Goodness of fit was evaluated by visual inspection with scaled residuals < 2 and goodness-of-fit p values > 0.1, and several models appeared to fit the data adequately. Benchmark concentration low (BMCL) values corresponding to the 5% response level ($BMCL_{05}$) for extra risk at the 95% confidence level were approximately 0.305-0.363 ppm for mild eye irritation and 0.611-0.652 ppm for moderate eye irritation, while $BMCL_{05}$ values for mild/moderate combined were slightly lower at 0.286-0.329 ppm (see Appendix A).

Eye irritation based on mild/moderate combined was selected as the endpoint of concern from Kulle et al. (1987, 1993). While several models had adequate goodness of fit, the probit and logistic models had lower (and similar) AIC values, indicating a better fit. The $BMCL_{05}$ values from these two models (0.286 and 0.316 ppm) were averaged to give a human point-of-departure value (POD_{HEC}) value of 0.30 ppm. This value is similar to the study NOAEL (0.5 ppm) at which 0% of the study participants responded. The California Environmental Protection Agency (CalEPA) calculated a similar $BMCL_{05}$ (0.44 ppm) based on the probit model and the Kulle et al. data for derivation of the final 1999 acute reference exposure level (REL) and the draft 2007 acute REL (CalEPA 1999, 2007).

Supporting Study - Lang et al. (2008)

The key studies are also supported by Lang et al. (2008), which had a reported NOAEL for eye irritation of 0.5 ppm for a 4-h exposure with no peak exposures. This reported NOAEL is higher than the LOAELs of 0.4 ppm from the two key studies. Lang et al. (2008) examined sensory irritation (objective and subjective measures), nasal flow and resistance, pulmonary function (e.g., PEF, FEV_1), reaction time, and personality factors in 21 healthy human subjects exposed for 4 h to 10 different exposure conditions. The exposure conditions included target formaldehyde concentrations of 0.15, 0.3, or 0.5 ppm, with or without four formaldehyde peaks of 0.6 or 1 ppm, and in the presence or absence of ethyl acetate (12-16 ppm) as an odorous masking agent (see Table 1 of Lang et al. 2008). The study data most applicable for supporting derivation of the acute ReV and ^{acute}ESL is that based on exposure without peaks, although a discussion of the results of exposure with peaks is also provided. Actual analytical exposure levels are reported in Table 6 of the study. Control exposure was either to 0 ppm formaldehyde or 0 ppm formaldehyde with the addition of ethyl acetate as an odorous masking agent, which was reported not to be an irritant at the concentrations used. The perception of odors may cause increased reporting of irritation due to insufficient distinction between olfactory stimulation and

trigeminal nerve-induced irritation. Objective measures of sensory irritation included ophthalmologic grading of conjunctival mucosa redness (e.g., 1=very slight to 4=severe) and blinking frequency (blinks per 90 seconds), and subjective measures included scores for eye/nose/respiratory irritation and olfactory symptoms (e.g., 1=slight to 5=very strong) as reported on complaint questionnaires (see Table 3 of Lang et al. 2008).

Exposures without peaks: There were no significant differences in nasal resistance/flow or pulmonary function. Decision reaction time in response to a visual and/or acoustic stimulus, but not motor reaction time (i.e., movement time), was significantly increased in the 0.3 ppm exposure group. However, this was not observed in any of the 0.5 ppm formaldehyde exposure groups and was not considered exposure-related. Reported eye irritation was significantly increased at 0.3 and 0.5 ppm formaldehyde as compared to the 0 ppm control exposure. However, reported eye irritation was not increased at 0.3 or 0.5 ppm formaldehyde as compared to the 0 ppm plus masking agent control exposure. Consequently, the study authors apparently did not consider 0.3 or 0.5 ppm formaldehyde as the LOAEL for eye irritation (i.e., the increased reporting could have been due to the perception of formaldehyde's odor). *The study authors report the NOAEL based on objective and subjective measures of eye irritation to be 0.5 ppm for exposure without peaks.*

Exposures with peaks: Nasal resistance/flow and pulmonary function did not show significant differences. Significantly increased nasal irritation was reported at 0.3 ppm with 0.6 ppm peaks (and 0.5 ppm with 1 ppm peaks) as compared to both control groups (i.e., 0 ppm formaldehyde and 0 ppm plus masking agent). Statistically increased conjunctival redness and blinking frequency were observed at 0.5 ppm with four 1 ppm peaks, but not in any of the 0.3 ppm formaldehyde groups. Eye irritation was significantly increased at 0.3 ppm with 0.6 ppm peaks (and 0.5 ppm with 1 ppm peaks) as compared to the 0 ppm plus masking agent control exposure. However, eye irritation at 0.3 ppm with 0.6 ppm peaks was not reported to also be significantly increased compared to the 0 ppm group, although it seems it should be based upon examination of Figure 7 of the study.

The finding of significantly increased reported eye irritation in the 0.3-0.6 ppm range in this study (i.e., 0.3 ppm with 0.6 ppm peaks compared to the 0 ppm plus masking agent control, 0.3 and 0.5 ppm compared to the 0 ppm control) lends support to the eye irritation LOAEL of 0.4 ppm from the Pazdrak et al. (1993) key study.

3.1.1.2.2 Animal Studies

Human studies are available and preferred over animal studies for calculation of the acute ReV and ^{acute}ESL. Therefore, this document focuses on relevant human studies (see above). Please refer to ATSDR (1999) for a discussion of short-term animal inhalation studies.

3.1.2 Metabolism and Mode-of-Action Analysis

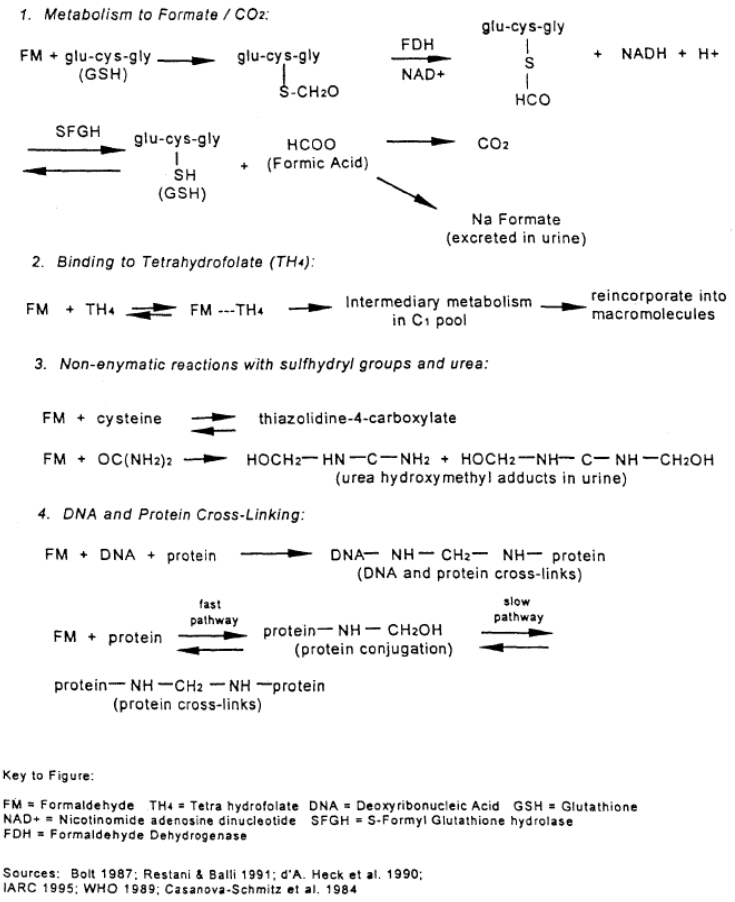
3.1.2.1 Metabolism

Formaldehyde is an essential metabolic intermediate in all cells. It is produced during the normal metabolism of serine, glycine, methionine, and choline and by the demethylation of N-, S-, and

O-methyl compounds. The metabolism of other chemicals (e.g., carbon tetrachloride, endrin, paraquat, dichloromethane, 2,3,7,8-TCDD) is also known to generate formaldehyde. Figure 1 (which is Figure 2-3 from ATSDR 1999) summarizes the metabolic pathways of formaldehyde biotransformation. Following endogenous production, formaldehyde is rapidly metabolized by formaldehyde dehydrogenase to formate (glutathione-dependent) in all tissues of the body and is quickly removed by the blood. Ultimately, formate is either excreted in the urine (primarily as formic acid), incorporated into other cellular molecules (e.g., purines, thymidine, and amino acids via the tetra-hydrofolate-dependent one-carbon biosynthetic pathways), or further oxidized to carbon dioxide and exhaled (ATSDR 1999). Most formate is oxidized to carbon dioxide and exhaled (Collins et al. 2001). IARC (2006) reports that while urinary levels of formate have considerable intra- and inter-individual variability, the average is about 12.5 mg/L. Neither formaldehyde nor formate are stored to any significant extent in any tissue of the body (ATSDR 1999).

Exogenous formaldehyde appears to be readily absorbed from the respiratory (and gastrointestinal) tract. More than 90% of inhaled formaldehyde is absorbed in the upper respiratory tract (IARC 2006a). Absorption appears to be limited to cell layers immediately adjacent to the point of contact. In rats, it is almost entirely absorbed in the nasal passages, while in monkeys, it is also absorbed in the nasopharynx, trachea, and proximal regions of the major bronchi (IARC 2006a). Formaldehyde dehydrogenase quickly metabolizes the formaldehyde-glutathione conjugate to formate. Due to rapid metabolism to formate by formaldehyde dehydrogenase, little (if any) formaldehyde can be found in the blood (ATSDR 1999). While there is inter-individual variability, the mean blood concentration prior to an inhalation exposure was reported to be 2.76 µg/g of blood in one study (Heck et al. 1985), and IARC (2006a) reports that the concentration of endogenous formaldehyde in human blood is about 2-3 mg/L. The Heck et al. (1985) study demonstrated that formaldehyde exposure in rats (14.4 ppm for 2 h) and humans (1.9 ppm for 40 minutes) did not significantly increase formaldehyde blood levels, indicating that appreciable absorption only occurred in tissues of the respiratory tract, absorbed formaldehyde was metabolized before reaching the bloodstream, and toxicity at distant sites (i.e., systemic toxicity) is unlikely. Additionally, Casanova et al. (1988) showed no differences between pre- and post-exposure Rhesus monkey blood formaldehyde levels following a 4-week exposure to 6 ppm, which the authors attributed to rapid local metabolism. Heck et al. (1982) showed that formaldehyde levels in the nasal mucosa of rats did not increase following subacute exposure (6 ppm, 6 h per day for 10 days), which might also be attributed to rapid metabolism. Formaldehyde not metabolized by formaldehyde dehydrogenase may form DNA-protein cross-links (Figure 1).

The glutathione-mediated metabolism of formaldehyde has been shown to be saturated in rats at exposure concentrations above 4 ppm, the approximate concentration where significant increases in cell proliferation, DNA-protein cross-links, and tumors begin to occur (NICNAS 2006). It is expected that this saturation contributes significantly to the nonlinearity of the induction of DNA-protein cross-links, nasal lesions, and nasal tumors at exposures above 5 to 6 ppm in the rat (CIIT 1999). The inhibition of DNA replication by DNA-protein cross-links is likely a major cause of formaldehyde-induced mutations (CIIT 1999), and has implications for the carcinogenic assessment (see Section 4.2.2.2). See ATSDR (1999) for additional information regarding formaldehyde metabolism.



Key to Figure:

FM = Formaldehyde TH4 = Tetra hydrofolate DNA = Deoxyribonucleic Acid GSH = Glutathione
NAD+ = Nicotinomide adenosine dinucleotide SFGH = S-Formyl Glutathione hydrolase
FDH = Formaldehyde Dehydrogenase

Sources: Bolt 1987; Restani & Balli 1991; d'A. Heck et al. 1990;
IARC 1995; WHO 1989; Casanova-Schmitz et al. 1984

Figure 1: Metabolic Pathways of Formaldehyde

3.1.2.2 Mode of Action (MOA) Analysis

An MOA is generally defined as a sequence of key events and processes (starting with interaction of an agent with a cell and proceeding through operational and anatomical changes) resulting in toxicity (USEPA 2005a). The toxicity of formaldehyde is route-dependent and irritation at the point of contact results from inhalation, oral, and dermal exposure. At sufficiently high air concentrations, formaldehyde and many other compounds are irritating to the eyes and respiratory tract. In regard to the MOA, irritation may be sensory and/or pathological in nature (Arts et al. 2006b). Chemically-induced sensory irritation involves interaction with local nerve endings (e.g., nervus trigeminus), and is also called chemosensory irritation or trigeminal stimulation. Sensory irritation can also involve the chemical stimulation of the vagal or glossopharyngeal nerves. The free nerve endings of the trigeminal system innervate the walls of the nasal passages and eyes and respond with, for example, nasal pungency or watery/prickly eyes to a large variety of volatile chemicals. Chemically-induced trigeminal nerve stimulation contributes to a sensation of general nasal and eye irritability, but does not necessarily lead to pathological changes such as cell or tissue damage (Arts et al. 2006b). Paustenbach (2000) defines sensory irritants as chemicals that produce temporary and undesirable effects on the eyes, nose, or throat. Sensory irritation induced by formaldehyde mainly consists of eye and nose irritation. Pathological irritation involves a localized pathological or pathophysiological response

(e.g., cell necrosis, tissue damage, hyperplasia, swelling, redness, pruritus (itching) or pain in a localized area of the respiratory tract) to a chemical (Arts et al. 2006b*). Sensory and pathological irritation are threshold effects which may occur in tissue at sites where formaldehyde is deposited and absorbed (i.e., points of contact).*

Most inhaled formaldehyde is deposited and absorbed in regions of the upper respiratory tract with which it first comes into contact. In obligate nose breathers (e.g., rats, mice), deposition/absorption occurs primarily in the nasal passages, while in oronasal breathers (e.g., monkeys, humans), it occurs in the nasal passages, oral cavity, trachea, and bronchus (Liteplo and Meek 2003). Since formaldehyde is highly reactive and cells at the site of contact are readily able to metabolize it (i.e., the ability of cells to metabolize formaldehyde is ubiquitous), inhalation and oral toxicity studies have generally found that formaldehyde's toxic effects are restricted to portal-of-entry tissue. Only under conditions where local detoxification capacity is overwhelmed would distant site effects be plausible (Collins et al. 2001). A mechanism through which distant site toxicity might be expressed is unclear. For example, exposure to relatively high concentrations (rats exposed to 14.4 ppm for 2 h, humans exposed to 1.9 ppm for 40 minutes) does not significantly increase blood levels (Heck et al. 1985). *Thus, toxicity at distant sites (i.e., systemic toxicity) is unlikely.*

3.1.2.3 Possible Mechanisms of Action

Mechanism of action, as opposed to MOA, is a more detailed understanding and description of events, often at the molecular level (USEPA 2005a). A general discussion on the possible mechanism(s) of action for formaldehyde toxicity, primarily taken from ATSDR (1999), is given below.

While the specific mechanism(s) of action by which formaldehyde may exert its irritant, corrosive, and cytotoxic effects are not known, relevant information is discussed here. Formaldehyde (and other aldehydes) are reactive and have a highly electronegative oxygen atom and less electronegative atoms of carbon. The carbonyl group is electrophilic and reacts readily with nucleophilic sites on cell membranes and amino groups in protein and DNA (Feron et al. 1991). Formaldehyde readily combines with free, unprotonated amino groups of amino acids to yield hydroxymethyl amino acid derivatives and a proton (H+), which is believed to be related to its germicidal properties. Higher concentrations precipitate protein (Loomis 1979). Either of these two mechanistic properties (i.e., reaction with free, unprotonated amino groups; precipitation of protein) or perhaps other unknown properties may be responsible for the formaldehyde-induced irritation. *It is probable that toxicity occurs when intracellular levels of formaldehyde saturate formaldehyde dehydrogenase activity, thereby overwhelming natural protection against formaldehyde and allowing unmetabolized formaldehyde to exert its effects locally.* High doses are cytotoxic and result in degeneration and necrosis of mucosal and epithelial cell layers, consistent with the hypothesis that toxic effects are mediated by formaldehyde itself and not the metabolites. Formaldehyde can also form DNA-protein cross-links *in vivo*.

See Section 2.4.2 of ATSDR (1999) for more detailed information on the possible mechanism(s) of action for formaldehyde-induced toxicity.

3.1.3 Dose Metric

In the key and supporting studies, data on formaldehyde air concentration are available. Formaldehyde air concentration is the most appropriate dose metric for the acute evaluation as concentration is the dominant determinant of irritation in acute exposure studies (TCEQ 2006).

3.1.4 Points-of-Departure (PODs) for the Key and Supporting Studies

The LOAEL of 0.5 mg/m^3 (0.4 ppm) (analytical concentration) from the Pazdrak et al. (1993) and Krakowiak et al. (1998) key studies will be used as the human equivalent concentration point-of-departure (POD_{HEC}) in calculation of the acute ReV and ESL. For the Kulle et al. (1987, 1993) study, the calculated $BMCL_{05}$ (0.30 ppm) is lower than the NOAEL (0.5 ppm) and will be used as the POD_{HEC} for supporting study calculations. For the Lang et al. (2008) supporting study, the reported NOAEL (0.5 ppm) will be used as the $POD_{HEC.}$

3.1.5 Dosimetric Adjustments

Since the acute irritant effects of formaldehyde appear to be primarily concentration dependent, exposure duration adjustments were not used to extrapolate from 2 h to 1 h for the key studies, or from 3 h and 4 h to 1 h for the supporting studies, consistent with TCEQ (2006).

Pazdrak et al. (1993) and Krakowiak et al. (1998) key studies:

POD_{HEC} = 0.5 mg/m^3 (0.4 ppm) (LOAEL)

Kulle et al. (1987) supporting study:

POD_{HEC} = 0.30 ppm ($BMCL_{05}$)

Lang et al. (2008) supporting study:

POD_{HEC} = 0.5 ppm (NOAEL)

3.1.6 Critical Effect and Adjustments of the POD_{HEC}

3.1.6.1 Critical Effect

The most sensitive endpoint for exposure to formaldehyde (short- and long-term) is irritation of the eyes and upper respiratory tract (i.e., nasopharyx, oral cavity, and throat), nose and throat irritation more specifically (ATSDR 1999). The specific critical effect of formaldehyde exposure in the key studies (Pazdrak et al. 1993 and Krakowiak et al. 1998) is sensory irritation, more specifically, eye and nose irritation and symptoms of rhinitis (e.g., increased itching, sneezing and congestion). The supporting studies by Kulle et al. (1987) and Lang et al (2008) also reported formaldehyde-induced eye (and nose) irritation.

3.1.6.2 Uncertainty Factors (UFs)

Sensory irritation is the critical effect of short-term formaldehyde exposure and is a threshold effect as discussed in the MOA analysis (Section 3.1.2.2). For noncarcinogenic effects which exhibit a threshold (i.e., nonlinear) MOA, a POD_{HEC} is determined and appropriate UFs are applied to derive a ReV.

The LOAEL from the Pazdrak et al. (1993) and Krakowiak et al. (1998) key studies (0.5 mg/m^3) was used as the POD_{HEC} and divided by the following uncertainty factors (UFs): 3 for extrapolation from a LOAEL to a NOAEL (UF_L), 3 for intrahuman variability (UF_H), and 1 for database uncertainty (UF_D) (total UF = 10). The UF for extrapolation from animals to humans (UF_A) is inapplicable and is assigned a value of 1 in the equation below. A UF_L of 3 was used since the LOAEL is considered minimal due to the mild symptoms observed (mild and reversible irritant effects; see Table E-2 of TCEQ 2006), and the clinical significance of changes in the nasal lavage fluid is uncertain. This is consistent with ATSDR (1999), which utilized a UF_L of 3 with Pazdrak et al. (1993) for use of a minimal LOAEL in calculating the acute inhalation MRL. A UF_H of 3 was used for intrahuman variability since the irritant effects were observed in studies which included potentially sensitive subpopulations (i.e., formaldehyde sensitized or potentially sensitized individuals). A UF_D of 1 was used because the overall toxicological database for formaldehyde is extensive. The acute database contains numerous inhalation studies in both humans and animals examining a range of potential formaldehyde-induced effects both more serious (e.g., nasal epithelial necrosis, hyperplasia, squamous metaplasia, increased cell proliferation, ciliary destruction) and less serious (e.g., eye, nose, throat irritation, small changes in pulmonary function) in nature. Several human studies have included potentially sensitive individuals (e.g., asthmatics), and among animal studies, several species/strains have been utilized (e.g., rats, mice, guinea pigs), including monkeys (ATSDR 1999).

The $BMCL_{05}$ based on Kulle et al. (1987, 1993) was used as a supporting POD_{HEC} with the following UFs: 10 for the UF_H, 1 for the UF_D, and 1 for the UF_L (total UF = 10). Consistent with TCEQ guidelines (TCEQ 2006), a UF_L of 1 was used since BMD modeling was performed. BMD modeling of the data was conducted at the 5% response level with 95% confidence, and the resulting $BMCL_{05}$ (0.30 ppm) was lower than the actual NOAEL (0.5 ppm). The UF_A is inapplicable and is assigned a value of 1 in the equation below. A value of 10 was used for the UF_H since the study did not include a potentially sensitive subpopulation (e.g., sensitized individuals, children), and the scientific literature indicates a broad range of reported susceptibility of humans to the irritating properties of airborne formaldehyde (ACGIH 2001). A UF_D of 1 was used because the overall toxicological database for formaldehyde is extensive.

The NOAEL based on Lang et al. (2008) was used as a supporting POD_{HEC} with the following UFs: 10 for the UF_H, 1 for the UF_D, and 1 for the UF_L (total UF = 10). A UF_L of 1 was used since the NOAEL was utilized as the POD_{HEC}. The UF_A is inapplicable and is assigned a value of 1 in the equation below. A value of 10 was used for the UF_H since the study did not include a potentially sensitive subpopulation (e.g., sensitized individuals, children), and the scientific literature indicates a broad range of reported susceptibility of humans to the irritating properties of airborne formaldehyde (ACGIH 2001). A UF_D of 1 was used because the overall toxicological database for formaldehyde is extensive.

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

As discussed in the previous section, UFs are applied to the POD_{HEC} from the key studies (Pazdrak et al. 1993 and Krakowiak et al. 1998) to derive the acute ReV.

Pazdrak et al. (1993) and Krakowiak et al. (1998) key studies:

acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 0.5 mg/m^3 / (3 x 1 x 3 x 1) =

0.05 mg/m^3 or 41 ppb

Kulle et al. (1987, 1993) supporting study:

acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 0.30 ppm / (10 x 1 x 1 x 1) = 0.030 ppm or 30 ppb

Lang et al. (2008) supporting study:

acute ReV = POD_{HEC} / (UF_H x UF_A x UF_L x UF_D) = 0.5 ppm / (10 x 1 x 1 x 1) = 0.05 ppm or 50 ppb

The acute ReV value based on the key studies was rounded to two significant figures at the end of all calculations. The rounded acute ReV was then used to calculate the ^{acute}ESL. Rounding to two significant figures, the 1-h acute ReV is 50 µg/m^3 (41 ppb) based on Pazdrak et al. (1993) and Krakowiak et al. (1998). At the target hazard quotient of 0.3, the ^{acute}ESL is 15 µg/m^3 (12 ppb) (Table 3).

Based on the $BMCL_{05}$ from the supporting Kulle et al. (1987, 1993) study, the calculated supporting acute ReV (30 ppb or 37 µg/m^3) and ^{acute}ESL (9 ppb or 11 µg/m^3) are similar. Similar supporting values would have also resulted from utilizing the NOAEL (0.5 ppm) from Kulle et al. (1987, 1993) as the POD_{HEC} (0.5 ppm / total UF of 10 = supporting acute ReV of 50 ppb and ESL of 15 ppb). Additionally, the supporting acute ReV (50 ppb) and ^{acute}ESL (15 ppb) based on Lang et al. (2008) are similar.

3.1.8 Comparison of Acute ReV to other Acute Values

The acute ReV (41 ppb) is almost identical to the acute MRL (40 ppb) by ATSDR (1999) and the national short-term investigation level (24-h concentration of 40 ppb) used by Australia in the interpretation of monitoring data and the nature/extent of public health risk (NICNAS 2006). It is slightly lower than the 1999 final acute REL and 2007 draft acute REL developed by CalEPA (1999, 2007), the 30-minute air quality guideline for Europe (WHO 2000), and the recommended short-term (e.g., hourly) ambient air (and indoor) standard for Australia (NICNAS 2006). The ^{acute}ESL (12 ppb) is the same as the Australian state environment protection policy level (1-h) used to evaluate air monitoring data (NICNAS 2006).

Table 3 Derivation of the Acute ReV and ^{acute}ESL

Parameter	Summary
Study	Pazdrak et al. (1993) and Krakowiak et al. (1998)
Study population	Pazdrak et al. (1993): 20 human volunteers (9 with skin hypersensitivity to formaldehyde); Krakowiak et al. (1998): 20 human volunteers (10 with bronchial asthma and suspected respiratory formaldehyde sensitization)
Study quality	medium
Exposure Methods	0.5 mg/m^3 (0.4 ppm) formaldehyde for 2 h
LOAEL	0.5 mg/m^3 (0.4 ppm)
NOAEL	None (0.5 ppm for the supporting study)
Critical Effects	Eye and nose irritation, symptoms of rhinitis
POD_{HEC}	0.5 mg/m^3
Exposure Duration	2 h
Extrapolation to 1 h	Not Applicable, effects concentration dependent
Extrapolated 1 h concentration	0.5 mg/m^3
Total UFs	10
Interspecies UF	*1*
Intraspecies UF	*3*
LOAEL UF	*3*
Incomplete Database UF	*1*
Database Quality	*high*
Acute ReV [1 h] (HQ = 1)	**50 µg/m^3 (41 ppb)**
Acute ESL [1 h] (HQ = 0.3)	**15 µg/m^3 (12 ppb)**

3.2. Welfare-Based Acute ESLs

3.2.1 Odor Perception

Formaldehyde has a pungent, suffocating, and highly irritating odor (ATSDR 1999). Nagata (2003) and Leonardos et al. (1969) have odor threshold information for formaldehyde and have been approved by TCEQ as references (see Appendix C of TCEQ 2006). Nagata (2003) lists a 50% odor detection threshold of 500 ppb (610 µg/m^3) for formaldehyde, and Leonardos et al. (1969) lists a recognition threshold of 1.2 mg/m^3 (1 ppm). Therefore, 500 ppb (610 µg/m^3) will be used as the $^{acute}ESL_{odor}$. Since odor is a concentration-dependent effect, the same $^{acute}ESL_{odor}$ is assigned to all averaging times.

3.2.2 Vegetation Effects

Mutters and Madore (1993) concluded that concentrations five times higher than previously observed peaks in and around urban areas will probably have no harmful effects on short-term

plant growth (i.e., concentrations up to about 365 ppb). Additionally, trees have a sufficient ability to absorb and rapidly metabolize formaldehyde and could act as an important sink for atmospheric formaldehyde (Kondo et al. 1996). In three tree species, exposure to concentrations as high as 2,000 ppb for 8 h did not produce visible foliar injury, consistent with other studies which showed no adverse effects on various plant species (e.g., spider plants, beans) exposed to short-term (e.g., 2-5 h) concentrations ranging from 400-10,000 ppb (Kondo et al. 1996). However, exposure to 2.88 mg/m^3 (2.4 ppm) for 1 h or 0.44 mg/m^3 (0.37 ppm) of formaldehyde for 5 h has been shown to decrease the pollen tube length of lily pollen grains (*Lilium longiflorum*). Exposure to 0.44 mg/m^3 (0.37 ppm) for 1 h, however, did not produce this effect (WHO 1989). Additionally, exposure to 700 ppb for 5 h was reported to cause foliar (leaf) lesions in alfalfa, but not spinach, endive, beets, or oats (Haagen-Smit et al. 1952). Exposure to 2,000 ppb for 2 h, however, was not reported to cause foliar injury in alfalfa, spinach, endive, beets, or oats. An $^{acute}ESL_{veg}$ was not developed since the 1-h concentration (2.4 ppm) and 2-h concentration (2 ppm) producing effects are significantly higher than the acute human health-based key study LOAELs discussed above (0.4 ppm), and the calculated acute ReV (41 ppb) and $^{acute}ESL$ (12 ppb) are significantly less than the short-term (1-5 h) levels discussed above which produced effects (370-2,400 ppb). Therefore, the acute ReV and $^{acute}ESL$ are expected to be protective of acute vegetative effects, and there is no need to develop an $^{acute}ESL_{veg}$ value. Additionally, based on historical data (1-h concentration range for 2001-2006 of approximately 0.4-69 ppb, 1-h mean < 10 ppb), short-term ambient air levels measured in Texas are not expected to approach phytotoxic levels.

3.3. Short-Term ESL and Values for Air Monitoring Evaluation

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

- acute ReV = 50 µg/m3 (41 ppb)
- acuteESL = 15 µg/m3 (12 ppb)
- acuteESLodor = 610 µg/m3 (500 ppb)

The short-term ESL for air permit reviews is the health-based $^{acute}ESL$ of 15 $\mu g/m^3$ (12 ppb) as it is lower than the $^{acute}ESL_{odor}$ (Table 1). The health-based $^{acute}ESL$ is used only for air permit reviews, and is not for the evaluation of ambient air monitoring data. For the evaluation of air monitoring data, the acute ReV of 50 $\mu g/m^3$ (41 ppb) is the lowest acute comparison value, although both the acute ReV and $^{acute}ESL_{odor}$ values may be used for the evaluation of air data (Table 1).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

4.1.1 Physical/Chemical Properties and Key Studies

Physical/chemical properties of formaldehyde are discussed in Chapter 3. In both human and animal noncarcinogenic studies, data suggest the most sensitive endpoint for long-term exposure to formaldehyde is irritation and associated respiratory symptoms. Since relevant human studies

are available and preferable over animal studies, human studies were reviewed and used to develop the chronic noncarcinogenic ReV. The long-term effects of formaldehyde in animals are discussed in ATSDR (1999).

Three studies were identified as providing PODs based on relevant and sensitive effects for calculation of the chronic noncarcinogenic ReV and ESL (chronicESLnonlinear(nc)). For reasons discussed in Section 4.1.7, Wilhelmsson and Holmstrom (1992) ultimately served as the key study with supporting calculations based on Holmstrom et al. (1989a) and Krzyzanowski et al. (1990). Other studies have also shown relationships between formaldehyde and eye/upper respiratory irritation at concentrations similar to those identified by the key and supporting studies (e.g., Broder et al. 1988a, 1988b, 1988c, Holness and Nethercott 1989, Ballarin et al. 1992, Olsen and Dossing 1982, Horvath et al. 1988).

Key Study - Wilhelmsson and Holmstrom (1992)

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

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

sensitivity to formaldehyde or related symptoms (e.g., clinical symptoms related to the upper and lower airways, eyes, or skin). However, the percent difference (22%) between atopics in the exposed and nonexposed groups suggests to the authors that atopics sensitive to formaldehyde may have left the formaldehyde-exposed group.

In regard to possible underlying mechanisms, the authors concluded that although formaldehyde can induce IgE-mediated type 1 reaction in the nose in certain circumstances, in most cases formaldehyde induces nasal discomfort through nonspecific/nonimmunological hyper-reactivity, which caused nasal discomfort in about 50% of the exposed population. For purposes of the study, they defined hyper-reactivity as significant nasal discomfort/obstruction in an environment where not all the exposed subjects experience annoying symptoms and allergic mechanisms can be ruled out. *The LOAEL and NOAEL from this study based on eye, nasal, and lower airway discomfort are 0.26 mg/m^3 (0.21 ppm) and 0.09 mg/m^3 (0.07 ppm), respectively.* Wilhelmsson and Holmstrom (1992) was used by CalEPA for derivation of the 1999 final chronic REL and the 2007 draft chronic REL (CalEPA 1999, 2007).

Supporting Study - Holmstrom et al. (1989a)

The supporting Holmstrom et al. (1989a) study compared histological changes in nasal tissue specimens from 70 chronically-exposed (mean of 10.4 years) chemical plant workers to those from 36 office workers. The median formaldehyde concentration for the chemical plant workers was 0.3 mg/m^3 (0.24 ppm), and the median concentration for the office workers was 0.09 mg/m^3 (0.07 ppm). A group of 100 furniture workers exposed to both formaldehyde and wood dust was also evaluated, with formaldehyde concentrations mostly between 0.2-0.3 mg/m^3 and wood dust mean levels between 1-2 mg/m^3. In addition to historical chemical factory data collected from 1979-1984, formaldehyde concentrations for all subjects were measured with personal sampling equipment (sampling tubes) in the breathing zone ambient air of worker stations. Smoking was not significantly different between the groups. Two nasal tissue specimens from the medial or inferior aspect of the middle turbinate were collected from each study participant. Changes in the nasal mucosa were classified histologically by a pathologist blindly (i.e., without knowledge of exposure) scoring the specimens on a grading scale of 0-8, with 0 being normal epithelium (see Table I of Holmstrom et al. 1989a).

The mean histological score for chemical workers (mean of 2.16) was significantly different than that of the reference (control) group (mean of 1.56). This was not the case for workers exposed to both formaldehyde and wood dust, which is a well-known irritant, causes both physiological and histological changes in the nasal mucosa, and has been reported to act as an additive carcinogen with formaldehyde (Holmstrom et al. 1989a). Loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently in chemical workers. There was no evidence of an association between histological score and duration of exposure, accumulated dose, or smoking. *The LOAEL and NOAEL from the supporting Holmstrom et al. (1989a) study based on subclinical histological effects indicative of mild nasal epithelial damage are 0.3 mg/m^3 (0.24 ppm) and 0.09 mg/m^3 (0.07 ppm), respectively.* Edling et al. (1988) also found histopathological changes in the nasal mucosa of workers chronically exposed to similar levels (and a high frequency of nasal symptoms), although no reliable LOAEL can be identified from the study. Holmstrom et al. (1989a) was used by ATSDR (1999) for derivation of the chronic inhalation MRL. *The key study of*

Wilhelmsson and Holmstrom (1992), along with this supporting study, suggests a LOAEL in the range of 0.26-0.3 mg/m^3 (0.21-0.24 ppm) for the irritant effects of formaldehyde in human occupational workers.

Supporting Study - Krzyzanowski et al. (1990)

The study population in the Krzyzanowski et al. (1990) supporting study included 298 children (6-15 years old) and 613 adults surveyed on standard chronic respiratory symptom questionnaires. Peak expiratory flow rates (PEFRs) were obtained each day, up to four times per day (morning, near noon, evening, bedtime) for two weeks by study participants trained on use of mini-Wright peak flow meters. PEFR is a measure of pulmonary function that represents the maximum flow of air attained during a forced expiratory maneuver, corresponding to the peak on a flow-volume curve. PEFR has been reported to be highly correlated with FEV_1 (Gautrin et al. 1994), and decreased PEFRs have been correlated with decreased FEV_1 in chronic obstructive lung disease (Berube et al. 1991) and with chronic respiratory symptoms (Cook et al. 1989). Additionally, PEFR decreases may be used in assessment of the severity of asthma symptoms (NAEPP 2007), and may be more predictive of severity level group under the NAEPP asthma guidelines than symptoms alone (Koshak 1999). For each week of the 2-week period, formaldehyde measurements were made by passive samplers in the kitchen, main living area, and each subject's bedroom. Mean exposure levels were grouped as ≤ 40 ppb, 41-60 ppb, and > 60 ppb.

Based on a random effects model, a significant relationship between decreased PEFRs and household formaldehyde levels was reported for children, with PEFR measurements (both morning and bedtime) decreasing linearly with increasing formaldehyde levels. Morning PEFR was further decreased in children with asthma. At 30 and 60 ppb, the estimated PEFR decrements in children were approximately 10% and 22%, respectively. PEFR decrements in children were not related to environmental tobacco smoke exposure. For adults, effects on PEFR were smaller (only morning PEFR was related to formaldehyde exposure), and occurred predominantly in smokers. Additionally, a statistically significant trend for increasing prevalence rates of physician-diagnosed chronic bronchitis and asthma with increasing formaldehyde concentration was reported for children, but only in those also exposed to environmental tobacco smoke. By contrast, no respiratory diseases in adults were significantly related to formaldehyde levels. The prevalence of self-reported chronic respiratory symptoms was not related to formaldehyde exposure for adults or children.

This study provides evidence, uncorroborated to date, that children may be more susceptible than adults to decreases in pulmonary function due to elevated formaldehyde in residential air. *While the clinical significance of these findings is uncertain (ATSDR 1999), TS selected the formaldehyde concentration cutoff of 60 ppb for the high exposure group for use as the LOAEL based on a 22% decrease in PEFR in children.* TS did not select 30 ppb as the LOAEL as it was associated with only a 10% decrease, and as an indicator of pulmonary function, a decrease in PEFR of ≤ 20% in asthmatics is indicative of good control (NAEPP 2007) and has been used to define "normal" in studies of chronic obstructive pulmonary disease (Jackson and Hubbard 2003).

4.1.2 MOA Analysis and Dose Metric

The MOA by which formaldehyde may produce noncarcinogenic effects (e.g., eye/respiratory irritation) is discussed in Section 3.1.2.2. For the key and supporting studies, data on formaldehyde air concentrations for residents and occupationally exposed workers are available. Formaldehyde air concentration is an appropriate dose metric for the chronic noncarcinogenic evaluation as air concentration is the dominant determinant of irritation in long-term studies (e.g., as opposed to blood concentration for example) (TCEQ 2006).

4.1.3 PODs for Key and Supporting Studies

The NOAEL from the Wilhelmsson and Holmstrom (1992) key study (0.09 mg/m^3 or 0.07 ppm) will be used as the occupational exposure concentration POD (POD_{OC}) in calculation of the chronic noncarcinogenic ReV and ESL ($^{chronic}ESL_{nonlinear(nc)}$). The NOAEL from the Holmstrom et al. (1989a) supporting study (0.09 mg/m^3 or 0.07 ppm) and the LOAEL from the Krzyzanowski et al. (1990) supporting study (60 ppb or 74 $\mu g/m^3$) will be used as PODs in calculation of supporting values. While the NOAEL from Wilhelmsson and Holmstrom (1992) is being used as the POD_{OC} value, TS notes that use of the LOAEL would result in chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values essentially identical to those derived using the NOAEL.

4.1.4 Dosimetric Adjustments

Because Wilhelmsson and Holmstrom (1992) and Holmstrom et al. (1989a) are occupational studies, the necessity to adjust occupational exposure levels to environmental exposure levels must be evaluated. The relationship between concentration and total dose (concentration times exposure duration) has been studied in experiments where rats were exposed to various concentrations and lengths of time such that the total inhaled dose was the same although exposure concentration varied. While some studies suggest concentration is more important than the product of concentration times duration in formaldehyde induction of epithelial damage in the upper respiratory tract (e.g., Wilmer et al. 1987, 1989, Swenberg et al. 1983), others suggest that cumulative dose may be important as effects are demonstrated with exposure levels over longer durations (e.g., Kamata et al. 1997, Kerns et al. 1983, Swenberg et al. 1980) that did not produce effects over shorter durations (e.g., see Wilmer et al. 1989 and CalEPA 1999). While there is uncertainty regarding whether an adjustment is necessary, the occupational POD_{OC} (0.09 mg/m^3) from Wilhelmsson and Holmstrom (1992) and Holmstrom et al. (1989a) was conservatively adjusted to a continuous exposure (see below). As Krzyzanowski et al. (1990) was a residential study, no such adjustment is necessary and the POD_{HEC} is 60 ppb.

Wilhelmsson and Holmstrom (1992) key study and Holmstrom et al. (1989a) supporting study:

$$POD_{HEC} = POD_{OC} \times (VE_{ho}/VE_{h}) \times (\text{days per week}_{oc}/\text{days per week}_{res})$$

where: VE_{ho} = occupational ventilation rate for an eight-hour day (10 m^3/day)

VE_h = nonoccupational ventilation rate for a 24-hour day (20 m^3/day)

$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)

$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per

week)

POD_{HEC} = 0.09 mg/m^3 x (10/20) x (5/7) = 0.032 mg/m^3 or 32 µg/m^3 (26 ppb)

Krzyzanowski et al. (1990) supporting study:

POD_{HEC} = 60 ppb

4.1.5 Critical Effect and Adjustments of the POD_{HEC}

4.1.5.1 Critical Effect

The most sensitive or critical endpoint for exposure to formaldehyde is irritation of the eyes and upper respiratory tract (e.g., nose and throat irritation) and associated symptomology. Tissues and organs distant from the portal-of-entry are spared toxic effects from formaldehyde levels normally expected in ambient and workplace air due to rapid and detoxifying metabolism (ATSDR 1999). The specific critical effects of formaldehyde exposure in the key study (Wilhelmsson and Holmstrom 1992) are increased rates of symptoms such as eye, nasal, and lower airway discomfort (e.g., cough, wheezing) in workers.

4.1.5.2 UFs

Section 3.1.2.2 discusses the MOA by which formaldehyde may produce toxicity. Determining a POD and applying appropriate UFs is used to derive a ReV for noncarcinogenic effects with a threshold/nonlinear MOA. Therefore, UFs were applied to the POD_{HEC} values from the key and supporting studies in deriving the chronic noncarcinogenic ReV. The POD_{HEC} (32 µg/m^3) from Wilhelmsson and Holmstrom (1992) and Holmstrom et al. (1989a) was divided by an intrahuman variability UF of 3 (UF_H) and a database UF of 1 (UF_D). Although the Wilhelmsson and Holmstrom (1992) key study included some potentially sensitive subpopulations (e.g., atopics, dermally-sensitized individuals), a value of 3 was used for the UF_H since there is a potential for a healthy worker effect (i.e., sensitive workers could have avoided jobs with formaldehyde), study data suggests atopics may have in fact left the formaldehyde-exposed group, and the scientific literature indicates a broad range of reported human susceptibility to the irritating properties of airborne formaldehyde (ACGIH 2001). A UF_H of 3 (as opposed to 10) was also used for the Holmstrom et al. (1989a) supporting study because although information is not presented which indicates the study population contained potentially sensitive subgroups, this study also had Wilhelmsson and Holmstrom as authors and seems to have drawn subjects from the same worker population (e.g., very similar number of exposed workers, identical number of controls, very similar mean ages, identical exposure concentration for controls), and greater sensitivity was not demonstrated in Wilhelmsson and Holmstrom (1992). A UF_D of 1 was selected because the overall toxicological database for formaldehyde is extensive (e.g., numerous human and rodent chronic studies evaluating a variety of respiratory, systemic, neurological, and immunological endpoints are available). Other UFs are not applicable (i.e., extrapolation from a LOAEL to a NOAEL, use of a subchronic study).

The POD_{HEC} (60 ppb or 74 µg/m^3) from the Krzyzanowski et al. (1990) supporting study was divided by a UF of 3 for extrapolation from a LOAEL to a NOAEL (UF_L), 1 for the UF_H, and 1 for the UF_D. A UF_L of 3 was applied to the LOAEL (60 ppb), which was associated with a PEFR

reduction of 22% in a random effects model, so that the resulting concentration (20 ppb) would correspond to an estimated PEFR decrement (7%) well below 20%. As an indicator of pulmonary function, a decrease in PEFR of ≤ 20% in asthmatics is indicative of good control (NAEPP 2007) and has been used to define "normal" in studies of chronic obstructive pulmonary disease (Jackson and Hubbard 2003). The resulting concentration of 20 ppb is also well below the cutoff concentration used for the reference (control) group (40 ppb). A value of 1 was used for the UF_H since the study included children (some with asthma), a potentially sensitive subpopulation. A UF_D of 1 was used because the overall toxicological database for formaldehyde is extensive.

4.1.6 Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$

As discussed in the previous section, UFs are applied to the POD_{HEC} values from the key and supporting studies in deriving the chronic noncarcinogenic ReV (Table 4).

Table 4 Comparison of UFs applied to the POD_{HEC}

PODHEC	Intra-Species UF	LOAEL-to-NOAEL UF	Database UF	Total UF	Reference Value
Key Study: Wilhelmsson and Holmstrom (1992) **Supporting Study:** Holmstrom et al. (1989a) 32 µg/m^3 (NOAEL)	3	1	1	3	11 µg/m^3 (8.9 ppb)
Supporting Study: Krzyzanowski et al. (1990) 60 ppb (LOAEL)	1	3	1	3	20 ppb (25 µg/m^3)

Rounding to two significant figures at the end of all calculations for the Wilhelmsson and Holmstrom (1992) key study yields a chronic noncarcinogenic ReV of 11 µg/m^3 (8.9 ppb). At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(nc)}$ is 3.3 µg/m^3 (2.7 ppb) (see Table 5). Use of the Holmstrom et al. (1989a) supporting study yields identical supporting values, and use of the Krzyzanowski et al. (1990) supporting study yields somewhat higher supporting values.

4.1.7 Comparison of Results

The supporting chronic ReV and $^{chronic}ESL_{nonlinear(nc)}$ values based on Holmstrom et al. (1989a) are identical to those based on the key study of Wilhelmsson and Holmstrom (1992), and supporting values based on Krzyzanowski et al. (1990) are very similar but slightly higher (by about a factor of two). While the Krzyzanowski et al. (1990) study has some desirable attributes, such as inclusion of a potentially sensitive subpopulation (children, including asthmatics) without the potential for a healthy worker effect and use of environmental (as opposed to occupational) exposure concentrations, TS believes there may be substantial uncertainty associated with the reported PEFR decrements which precludes its use as a key study. For

example, there is wide variability in the published reference values for PEFR (NAEPP 2007), PEFR varies with factors such as gender, age, and height (Boezen et al. 1994, Quackenboss et al. 1989), and no information was presented in the study to demonstrate that the reference (control) and exposure groups would be expected to have similar PEFRs in the absence of formaldehyde exposure. However, Krzyzanowski et al. (1990) is valuable as a supporting study for comparison of calculated values to those based on the key study. The chronic ReV (8.9 ppb) based on the selected key study is similar to ATSDR's chronic inhalation MRL (8 ppb) and CalEPA's 2007 draft chronic REL (7 ppb), and the $^{chronic}ESL_{nonlinear(nc)}$ (2.7 ppb) is similar and CalEPA's 1999 final chronic REL (2 ppb).

Table 5 Derivation of the Chronic Noncarcinogenic ReV and $^{chronic}ESL_{nonlinear(nc)}$

Parameter	**Summary**
Study	Wilhelmsson and Holmstrom (1992)
Study Population	66 exposed workers, 36 controls
Study Quality	high
Exposure Levels	0.26 mg/m^3 for workers 0.09 mg/m^3 for controls
Critical Effects	elevated rates of symptoms such as eye, nasal, and lower airway discomfort
POD_{OC} (NOAEL)	0.09 mg/m^3
Exposure Duration	5 days per week, 10 years (mean)
Extrapolation to continuous exposure (POD_{HEC})	0.032 mg/m^3 (32 µg/m^3)
Total UFs	3
Interspecies UF	*NA*
Intraspecies UF	*3*
LOAEL-to-NOAEL UF	*1*
Subchronic to chronic UF	*NA*
Incomplete Database UF	*1*
Database Quality	*high*
Chronic Noncarc. ReV (HQ = 1)	**11 µg/m^3 (8.9 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**3.3 µg/m^3 (2.7 ppb)**

4.2 Carcinogenic Potential

4.2.1 Carcinogenic Weight of Evidence

4.2.1.1 WOE Classifications by Various Agencies and Recent Data

ATSDR (1999) provides the following general discussion of the WOE classifications for formaldehyde by various agencies.

> Several studies of laboratory rats exposed for life to high amounts of formaldehyde in air found that the rats developed nose cancer. Some studies of humans exposed to lower amounts of formaldehyde in workplace air found more cases of cancer of the nose and throat (nasopharyngeal cancer) than expected, but other studies have not found nasopharyngeal cancer in other groups of workers exposed to formaldehyde in air. The Department of Health and Human Services (DHHS) has determined that formaldehyde may reasonably be anticipated to be a human carcinogen (NTP). The International Agency for Research on Cancer (IARC) has determined that formaldehyde is probably carcinogenic to humans. This determination was based on specific judgments that there is limited evidence in humans and sufficient evidence in laboratory animals that formaldehyde can cause cancer. The Environmental Protection Agency (EPA) has determined that formaldehyde is a probable human carcinogen based on limited evidence in humans and sufficient evidence in laboratory animals.

However, a more recent collaborative review of the data by USEPA and the Chemical Industry Institute of Toxicology (CIIT 1998) appeared to take a less certain position and concluded that, "it appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out." (ATSDR 1999)

In regard to formaldehyde being classified as a human carcinogen by regulatory agencies, HEI (2007) interprets human evidence as weak and inconsistent. Health Canada (2001) did not assign a carcinogenic classification to formaldehyde, but stated the conditions under which formaldehyde is considered to represent a carcinogenic hazard, "Based primarily upon data derived from laboratory studies, therefore, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans."

Since ATSDR (1999) was published, IARC has recategorized formaldehyde as carcinogenic to humans (Group 1) based on sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans (IARC 2004, 2006b). Evidence for cancer of the nasal cavity and paranasal sinuses and leukemia in humans was not considered sufficient at the time the IARC monograph was published in December 2006 (IARC 2006b). A key part of IARC (2006b) considering human data sufficient was the excess nasopharyngeal cancer observed in the 10-plant National Cancer Institute (NCI) cohort study of formaldehyde-exposed workers (Hauptmann et al. 2004). In Hauptmann et al. (2004), peak exposure of 4 ppm and higher was found to increase the incidence of nasopharyngeal cancer (Arts et al. 2006a). Marsh and Youk (2005) reanalyzed the NCI data and showed that the reported exposure-response for peak exposure was primarily the result of six cancer deaths from Plant 1 (there were only 10 nasopharyngeal cancers across all ten plants). In fact, plant 2-10 workers had a 35% deficit in nasopharyngeal cancer mortality. A recent second reanalysis (Marsh et al. 2007a) suggests that NCI did not explicitly account for an important interaction between plant group (plant 1 versus plants 2-10) and peak formaldehyde exposure which prohibits a generalization of formaldehyde effects both within and beyond the NCI cohort.

Additionally, a recent nested case-control study (Marsh et al. 2007b) of nasopharyngeal cancer in plant 1 workers suggests that the large nasopharyngeal cancer excess may not be due to formaldehyde exposure but rather may reflect the influence of external employment in metal industries with possible exposures to suspected risk factors for upper respiratory cancer (e.g.,

sulfuric acid mists, mineral acid, metal dusts). Updated epidemiological studies from NCI are expected in 2008. The recent 2007 studies mentioned above, and obviously the updated NCI studies yet to be released, were not available for review in 2006, may have impacted the IARC (2006b) evaluation and designation of formaldehyde as carcinogenic to humans, and may eventually affect the carcinogenic classification of formaldehyde by other agencies as well.

4.2.1.2 Human Data on Specific Cancer Types

Possible associations between formaldehyde exposure and various cancers have been examined extensively in epidemiological studies (e.g., cohort, case control) of occupationally-exposed workers, both industrial (e.g., formaldehyde production workers) and professional (e.g., pathologists). More than 25 cohort studies and more than 15 case-control studies have examined the association between formaldehyde and cancer (see Tables 16 and 17 of IARC 2006b).

4.2.1.2.1 Lung Cancer

Based on epidemiological studies of exposed workers, little evidence exists of a possible association between formaldehyde exposure and lung cancer (e.g., Coggan et al. 2003, Chiazze et al. 1997), and traditional criteria of causality such as consistency and strength of association and exposure-response are not fulfilled (Liteplo and Meek 2003, Health Canada 2001). For example, Hauptmann et al. (2004) found no association with lung cancer in a cohort of 25,619 US workers, and is consistent with several other fairly recent studies (Pinkerton et al. 2004, Collins et al. 1997, Marsh et al. 2001, Youk et al. 2001). In fact, lung cancer mortality in Hauptmann et al. (2004) decreased with exposure duration and cumulative exposure, and respiratory cancer risk in Pinkerton et al. (2004) decreased with duration of employment and time since first exposure (IARC 2006b). Additionally, Bond et al. (1986) reported a negative association between formaldehyde exposure and lung cancer mortality, and Partanen et al. (1990) reported less than expected lung cancer with odds ratios adjusted for smoking (IARC 2006b). Acheson et al. (1984) concluded that their reported results are against the view that formaldehyde is a lung carcinogen, and Andjelkovich et al. (1995a, 1995b) found no association between formaldehyde exposure and malignancies of the respiratory system. Based on available data, TS cannot conclude that formaldehyde causes lung cancer.

4.2.1.2.2 Leukemia

The biological plausibility of formaldehyde possibly being associated with an increased risk of lymphohematopoietic malignancies such as leukemia in occupationally-exposed workers is currently a debate within the scientific community. While increased risks of non-respiratory tract cancers (e.g., leukemia in Hauptmann et al. 2003 and Pinkerton et al. 2004) have been reported only sporadically with little consistent pattern (Liteplo and Meek 2003, Health Canada 2001), a hypothetical MOA has been proposed at some toxicology and risk assessment conferences, though not published. The hypothetical MOA requires that B lymphocytes or hematopoietic progenitor cells in the nasal-associated lymphoid tissue (NALT) undergo formaldehyde-induced mutagenic change at the POE, leading to a sustained malignant transformation, then migration back to the bone marrow or primary lymphatic tissue, ultimately producing a lymphohematopoietic malignancy (Pyatt et al. 2008). A thorough discussion of the diverse subjects and data relevant to evaluation of the hypothetical MOA is outside the scope of this

document. However, based on available information, TS considers formaldehyde-induced leukemia in occupationally-exposed workers to be of dubious biological plausibility. Some basic information and study conclusions relevant to this determination are presented below, but the reader is referred to the referenced studies for detailed information and discussions.

A recent evaluation (Pyatt et al. 2008) indicates that available scientific data do not support the proposed hypothetical MOA or the notion that formaldehyde can cause lymphohematopoietic malignancies (e.g., epidemiological and animal bioassay data, known etiology and risk factors for such malignancies, lack of demonstrated inhaled formaldehyde-induced hematotoxicity). For example, rats and mice also have NALT, but animal studies have not demonstrated that chronic, high-dose inhalation (or oral) exposure to formaldehyde causes hematopoietic toxicity or malignancies. Non-Hodgkin's lymphoma (NHL) arising in the NALT would likely be the primary malignancy observed if the hypothesized MOA were operative, but nasal lymphomas are absent in studies of occupationally-exposed workers. Study results with formaldehyde are in contrast to studies with established leukemogenic agents, which produce dose-related hematotoxicity, bone marrow hypoplasia, reproducible hematopoietic malignancies in rodents, etc. In other words, formaldehyde does not meet the key fundamental characteristics for leukemogenic chemicals, which concern the ability to reach the bone marrow and induce hematotoxicity. Additionally, the critical assumptions necessary for the hypothesized MOA to be operative (e.g., inhalation exposure would have to result in the direct contact of formaldehyde with immune cells in the NALT, circumventing the necessity for distant site toxicity) are not supported by experimental data, and the hypothesized MOA does not meet the explicit USEPA criteria for evaluation of an MOA (see Table 1 of Pyatt et al. 2008). Pyatt et al. (2008) concluded that existing science does not support the proposed hypothetical MOA as a logical explanation for proposing that formaldehyde is a realistic etiological factor for any lymphohematopoietic malignancy (e.g., leukemia). Furthermore, a possible link with leukemia has been reported not to fulfill traditional criteria for causality (e.g., consistency, biological plausibility) (Liteplo and Meek 2003, Health Canada 2001), and several researchers have discussed the biological implausibility (e.g., Heck and Casanova 2004, Golden et al. 2006, Collins 2004, Schmid and Speit 2007) or improbability (e.g., Cole and Axten 2004, Collins and Lineker 2004, Marsh and Youk 2004, Casanova et al. 2004) of such an association. For example, Heck and Casanova (2004) conducted an extensive review and concluded that it is highly unlikely that formaldehyde is leukemogenic.

On the other hand, Hauptmann et al. (2003) reported an association of leukemia with peak exposure, and with average exposure intensity and exposure duration to a lesser degree (but not cumulative exposure). However, most of the relative risk confidence intervals (22 out of 24) for the types of leukemia evaluated include 1 (see Tables 3, 4, and 6 of Hauptmann et al. 2003), which could be indicative of no excess risk, and the authors suggest caution in drawing conclusions regarding an association with leukemia. Marsh and Youk (2004) reanalyzed leukemia risk from Hauptmann et al. (2003) and indicated that the elevated leukemia and myeloid leukemia risks reported in the higher exposure categories (and reported trends for highest peak and average intensity of exposure) occurred because of comparison with statistically significant leukemia and myeloid leukemia death deficits in the baseline category used to calculate relative risk (least exposed worker referent group). Similar deficits occurred in unexposed workers. Additionally, the study authors indicated that the weak association between leukemia and duration of exposure reported by Hauptmann et al. (2003) was not robust as

exposure recategorization produced no evidence of an association, and the association for average exposure intensity was only weakly robust. Leukemia and myeloid leukemia risk does not appear to be elevated or increase with increasing duration of time worked in a highest peak category or with increasing highest peak exposure given the same duration (see Table 6 in Marsh and Youk 2004), with essentially the same findings for average exposure intensity (see Tables 7 and 8). For Pinkerton et al. (2004), all standardized mortality ratio confidence intervals for the leukemia types evaluated include 1 (see Table 3 of Pinkerton et al. 2004). Additionally, Coggan et al. (2003) reported lower than expected leukemia among the highly-exposed workers (IARC 2006b).

Despite unpersuasive and conflicting study findings and biological implausibility considerations, IARC (2006b) interprets available data as being strong but not sufficient evidence for a causal association between leukemia and formaldehyde. However, overall, available data do not support formaldehyde as being leukemogenic (NICNAS 2006, Naya and Nakanishi 2005, Pyatt et al. 2008). TS interprets currently available epidemiological data as being weak and insufficient in regard to formaldehyde causing leukemia, and considers formaldehyde-induced leukemia in occupationally-exposed workers to be of dubious biological plausibility based on available information (e.g., rapid metabolism at the site of contact, limited ability to increase blood concentrations). However, TS will re-evaluate these issues as new data become available.

4.2.1.2.3 Nasal and Nasopharyngeal Cancer

For nasal and nasopharyngeal cancer, which is relatively rare in humans, there is inconsistent evidence of an association based on cohort studies (from which there has been little evidence of an exposure-response relationship) (Liteplo and Meek 2003, Monticello and Morgan 1997, Health Canada 2001). For example, risk for nasopharyngeal cancer (most often squamous cell carcinoma) was not increased in a study of anatomists (Stroup et al. 1986) or mortuary workers (Hayes et al. 1990), in a study of 14,014 chemical/plastic factory workers (6 plants) in the United Kingdom (Coggan et al. 2003, Gardner et al. 1993), in a study of 11,039 (82% female) US garment factory workers (Pinkerton et al. 2004, a follow-up to Stayner et al. 1985b and 1988, a.k.a. the NIOSH cohort), or in 3,929 iron foundry workers (Andjelkovich et al. 1995a).

On the other hand, increased risk for nasopharyngeal cancer was reported in a cohort study of 26,561 workers (10 plants) in the United States, with relative risks increased for average exposure intensity, cumulative exposure, highest peak exposure, and exposure duration (Hauptmann et al. 2004, a follow-up of Blair et al. 1986 and 1990c). Subsequent analyses of this large US cohort (a.k.a. the NCI cohort) have found that the increased risk was primarily the result of six cancer deaths from plant 1, and that plant 2-10 workers had a 35% deficit in nasopharyngeal cancer mortality (Marsh and Youk 2005). For exposed workers in NCI plants 2-10, about 3 deaths (3.15) were expected compared to 2 observed (Tarone and McLaughlin 2005). On the other hand, less than 1 death (0.66) was expected for plant 1 of the NCI study, and 6 were observed. The magnitude of the difference between the standardized mortality ratio (SMR) for plant 1 exposed workers (9.1) versus plant 2-10 workers (0.6), especially considering that 3 of the 6 nasopharyngeal cancer deaths from plant 1 occurred in workers exposed to formaldehyde for less than 8 months, raise doubt concerning the interpretation of risk estimates from Hauptmann et al. (2004) as supporting an association between formaldehyde and nasopharyngeal cancer (Tarone and McLaughlin 2005).

Because of the large difference in SMRs, plant 1 workers have been studied more closely in regard to other possible exposures (silver smithing/other metal work). Studies of plant 1 workers have found that three of the four original nasopharyngeal cases in plant 1 had prior employment in jobs involving exposure to metal fumes or dust (Marsh and Youk 2005), and that the large nasopharyngeal cancer excess in plant 1 workers may reflect the influence of external employment in metal industries with possible exposures to suspected risk factors for upper respiratory cancer (e.g., sulfuric acid mists, mineral acid, metal dusts) (Marsh et al. 2007b, Marsh et al. 2002). There was a 14-fold increased nasopharyngeal cancer risk associated with silver smithing for plant 1 workers, and over a 7-fold increase for silver smithing/other metal work (see Table 4 of Marsh et al. 2007b). Across the British, NIOSH, and NCI (plants 2-10) cohort studies, approximately 6 nasopharyngeal cancer deaths (6.11) were expected versus 3 observed, two times fewer nasopharyngeal cancer deaths than expected (Tarone and McLaughlin 2005).

In three case-control studies (Vaughan et al. 1986, Roush et al. 1987, West et al. 1993), significantly increased risks of nasopharyngeal cancer were observed in workers with the highest levels or duration of exposure. In three other studies of nasal squamous cell carcinoma, either a nonsignificant increase (Hayes et al. 1990, Olsen and Asnaes 1986) or no increase (Luce et al. 1993) was found. All these case-control studies are considered to have limitations. For example, measures of exposure are less reliable in these population-based investigations than in the larger and more extensive cohort studies, and methodological limitations complicate the interpretation of several of these studies (Liteplo and Meek 2003, Health Canada 2001). As opposed to distant site cancers (e.g., leukemia), nasal and nasopharyngeal cancer would be portal-of-entry cancers and more biologically plausible based on formaldehyde's high water solubility, reactivity, rapid metabolism at the site of contact, and limited ability to increase blood concentrations.

While epidemiological studies are inconsistent and, as a whole, do not provide strong evidence, the possibility of a causal association between formaldehyde exposure and an increased risk of upper respiratory cancer in humans cannot be excluded (Liteplo and Meek 2003, NICNAS 2006, Health Canada 2001).

4.2.1.3 Animal Data

As mentioned previously, formaldehyde is known to induce cancer in laboratory animals. There is indisputable evidence that inhalation exposure is carcinogenic to rats, with tumors being limited to the site of contact (nasal passages) (Liteplo and Meek 2003, Health Canada 2001). Formaldehyde concentrations ranging from approximately 6 to 15 ppm increased the incidence of nasal tumors in three bioassays with Fisher 344 rats (Kamata et al. 1997, Monticello et al. 1996, Kerns et al. 1983 and Swenberg et al. 1980). See *Animal Cancer Studies* in Section 2.2.1.8 of ATSDR (1999) for a detailed description of these three bioassays, as only a general discussion is provided here. Nasal squamous cell carcinoma was the main cancer found (82% of the cancers in these three studies), although nasal polyploid adenoma (15%), buccal squamous cell carcinoma (2%), and squamous cell papilloma (1%) were also found. No malignant nasal tumors were induced at concentrations of 2 ppm and lower (ATSDR 1999). The exposure-response relationship is similar across rat studies and highly nonlinear, with sharp increases in tumor incidence occurring only at concentrations greater than 6 ppm. Nasal tumors are markedly increased only in rats exposed to long-term formaldehyde concentrations in the range of

approximately 10 to 15 ppm (Liteplo and Meek 2003, Health Canada 2001). Available mouse data from Kerns et al. (1983) indicate that mice are less sensitive than rats to formaldehyde-induced cancers, which may be due to a more efficient reduction in minute volumes during formaldehyde exposures (ATSDR 1999, Chang et al. 1981, 1983). Despite that the nasal anatomy, air flow, and breathing patterns (nasal versus oronasal) of rats and humans are markedly different, in 1991 USEPA utilized the Kerns et al. (1983) rat study (conducted for CIIT) to calculate the current unit risk factor (URF) on the Integrated Risk Information System (IRIS).

4.2.2 Carcinogenic MOA

A carcinogenic MOA is a sequence of key events and processes (starting with interaction of an agent with a cell and proceeding through operational and anatomical changes) resulting in cancer formation. A key event is an empirically observable precursor step that is itself a necessary element of the MOA or is a biologically-based marker for such an element. There are many examples of possible carcinogenic MOAs, such as mutagenicity, cytotoxicity with reparative cell proliferation, mitogenesis, inhibition of cell death, and immune suppression (USEPA 2005a). *Sustained cytotoxicity with reparative cell proliferation is a carcinogenic MOA considered particularly relevant to formaldehyde.*

4.2.2.1 Relevant Data

Animal studies provide the vast majority of data relevant to the carcinogenic MOA for formaldehyde. A brief summary of some of the most important information is provided here.

Based on animal data, it may be concluded that nasopharyngeal cancer is found only at high formaldehyde levels, that is, those associated with cytotoxicity, tissue damage, and repair (restorative hyper- and meta-plasia) of the respiratory epithelium (Arts et al. 2006b). In other words, the findings from rat studies indicate that formaldehyde induces nasal cell carcinomas at exposure concentrations causing severe damage to the nasal epithelium. Exposure concentrations of about 6 ppm (and higher) have been shown to cause severe nasal epithelial damage (i.e., cytotoxicity/cell necrosis) in rats, generally leading to restorative hyperplasia (Arts et al. 2006a). Similar exposure concentrations (approximately 6-7 ppm) have been reported as BMC_{10} values in a recent subacute genomics study of rat nasal epithelium for gene ontology categories associated with the presumed MOA, including cell proliferation (e.g., mean BMC_{10} of 5.68 ppm for expression changes in 182 genes in the "positive regulation of cell proliferation" gene ontology category) (Thomas et al. 2007). Even at concentrations of around 6 ppm, formaldehyde has induced only a very low incidence of nasal squamous cell carcinoma in rats. In Kerns et al. (1983), 5.6 ppm induced nasal squamous cell carcinoma in 2 of 235 animals, and in Monticello et al. (1996), 6.0 ppm induced nasal squamous cell carcinoma in only 1 of 90 animals. While slight respiratory epithelial hyperplasia and metaplasia were seen in rats exposed to 2-3 ppm, it was without the occurrence of nasal tumors (Arts et al. 2006b). *Thus, severe damage to the nasal mucosa may be a prerequisite for formaldehyde-induced nasal tumors as an increased incidence of nasal cell carcinoma is seen concurrent with clearly cytotoxic effects (Arts et al. 2006a).* For example, Woutersen et al. (1989) found that the high incidence of nasal squamous cell carcinomas (26%) at 9.8 ppm over 28 months of exposure occurred only in animals with a mechanically-induced, severely-damaged nasal mucosa (i.e., not in those exposed to 9.8 ppm

with initially intact nasal mucosa).

While concentrations of around 6 ppm have been shown to cause nasal epithelial damage and a very low incidence of nasal squamous cell carcinoma, sharp increases in nasal epithelial damage/cell proliferation and tumor incidence only occur at greater concentrations (Liteplo and Meek 2003, Health Canada 2001). More specifically, nasal tumors are markedly increased only in rats exposed to chronic formaldehyde concentrations in the range of about 10 to 15 ppm, where cell proliferation resulting from cytotoxicity is also markedly increased. Available limited data show that sustained cytotoxicity and regenerative proliferation were observed in the nasal cavities of rats exposed subchronically (3 months) to concentrations which induced nasal tumors in cancer bioassays, but the converse is not always true (see Table 3 of Liteplo and Meek 2003). In other words, regenerative proliferation was found at all concentrations which induced tumors, but tumors were not always found at all concentrations which induced proliferation. *This information suggests that sustained cytotoxicity-induced regenerative proliferation of the nasal epithelium may be a prerequisite, but may not be sufficient, for formaldehyde-induced nasal tumors.*

Sustained cytotoxicity-induced regenerative proliferation of the nasal epithelium have not been observed in rats exposed to 2 ppm or less, regardless of exposure period (e.g., acute versus chronic), and these effects appear to be more closely related to concentration than total cumulative dose (i.e., concentration times duration) (Liteplo and Meek 2003, Health Canada 2001). A formaldehyde level of 1 ppm has been considered a NOAEL for nasal injury in long-term animal toxicity studies (Arts et al. 2006b). Some additional information relevant to the carcinogenic MOA for formaldehyde is discussed below.

4.2.2.2 Carcinogenic MOA

ATSDR (1999) provides the following general discussion on formaldehyde's carcinogenic MOA.

> Several key points or events determine the mechanism by which formaldehyde induces cancer in rats. First, a single high dos□e (40 ppm) for acute durations is not likely sufficient to induce squamous cell carcinoma cancer (Bhalla et al. 1990; Monteiro-Riviere and Popp 1986; Wilmer et al. 1987); repeated exposures for protracted durations are required to induce nasal cancer in rats. Second, the data indicate that a sequence of cellular events must occur in order to induce nasal carcinomas. The induction of nasal cancer in rats by formaldehyde requires repeated exposure for prolonged periods of time to high concentrations that are both irritating and that cause cell damage to a population of the nasal mucosa cells lining the nose. Exposure to high concentrations for prolonged periods during inhalation exposure overwhelms or otherwise exhausts the inherent defense mechanisms to formaldehyde (mucociliary clearance, FDH, DNA repair). This cellular and tissue damage inflicted by unmetabolized formaldehyde is then followed by a regenerative hyperplasia and metaplasia phase (Chang et al. 1983; Feron et al. 1988; Rusch et al. 1983; Wilmer et al. 1987; Woutersen et al. 1987, 1989), which results in increased cell-turnover rates within the mucosa. Formaldehyde has been demonstrated to be genotoxic in some (but not all) cell lines and test systems (Basler et al. 1985; Donovan et al. 1983; Grafstrom et al. 1985, 1993; Rithidech et al. 1987; Snyder and Van Houten

1986; Valencia et al. 1989; Woodruff et al. 1985; Yager et al. 1986). DNA-protein cross-links have been demonstrated in experimental animals after inhalation exposure to formaldehyde and can cause mutation or chromosomal aberrations if not repaired prior to cell replication. The DNA damage that occurs in these altered cells is carried into subsequent cell populations and thereby greatly enhances the progression of preneoplastic cells to cancer. In this manner, formaldehyde likely can act as a complete carcinogen (providing initiation, promotion, and progression) with repeated and prolonged duration of exposure at cytotoxic concentrations.

4.2.2.2.1 Role of Sustained Cytotoxicity, Regenerative Proliferation, and DNA-Protein Cross-Links in Tumorigenesis

Formaldehyde is highly cytotoxic, and based on available data, it has been hypothesized that a sustained increase in nasal epithelial cell regenerative proliferation resulting from cytotoxicity is a requisite precursor in the MOA for the induction of tumors. Tumors were observed only at concentrations which caused sustained cytotoxicity and regenerative proliferation, and increased DNA-protein cross-links, in subchronically exposed rats (see Section 4.2.2.1). Furthermore, there is concordance in the incidence of these three endpoints (i.e., cytotoxicity/proliferation, DNA-protein cross-links, tumors) across regions of the nasal passages. That is, tumors and increased cytotoxicity-induced proliferation/DNA-protein cross-links are found in similar regions of the nasal passages. The exposure-response relationships for these three endpoints are highly nonlinear, with significant increases occurring at 4 ppm. This shows good agreement with the concentrations where glutathione-mediated metabolism is saturated (4 ppm) and mucociliary clearance is inhibited (> 2 ppm) (NICNAS 2006).

Regenerative cell proliferation may convert DNA adducts into mutations before DNA repair can occur and may be viewed as a necessary, but not always sufficient, event for tumor formation. Cytotoxicity-induced cell proliferation is the fundamental obligatory step in the carcinogenic process for carcinogens with a nongenotoxic-cytotoxic MOA, and no increased cancer risk would be expected for such chemicals at sub-cytotoxic concentrations (Butterworth et al. 1995). The Australian Department of Health and Ageing (DHA), for example, indicates that regenerative cell proliferation associated with cytotoxicity appears to be an obligatory step in formaldehyde-induced cancer, the most significant determinant of neoplastic progression, and considers them key precursor events. Nasal cancer does not occur in rats at concentrations which do not significantly increase cell proliferation (Monticello and Morgan 1997). Additionally, there is good correlation between key events and regional tumor incidence/sites (NICNAS 2006). For example, in Monticello et al. (1996), rat tumor rate was highly correlated (R^2=0.88) with population-weighted unit-length labeling index (ULLI), which is a measure of cell proliferation that takes into account the number of cells at the site of interest (i.e., target cell population size) (Monticello and Morgan 1997). Liteplo and Meek (2003) and Health Canada (2001) concluded that the degree of confidence in regenerative proliferation being an obligatory step in formaldehyde-induced nasal tumors in rats is moderate to high, and based on available data, TS concurs.

4.2.2.2.2 Role of Genotoxicity and Mutation

In addition to cytotoxicity-induced cell proliferation, genotoxicity and mutation, for which DNA-

protein cross-links may serve as a marker, may also play a role in formaldehyde-induced carcinogenesis in nasal tissue (Liteplo and Meek 2003, Health Canada 2001). DNA-protein cross-links are potentially useful markers of genotoxicity and mutagenic potential because they may initiate DNA replication errors, which may result in mutation (IARC 2006a). The exposure-response for DNA-protein cross-links is highly nonlinear, with a sharp increase at concentrations higher than 4 ppm and without accumulation on repeated exposure (Liteplo and Meek 2003, Health Canada 2001). The use of DNA-protein cross-links as a dosimeter in cancer target tissues is supported by correlative observations of the relationship between formaldehyde air concentration and DNA-protein cross-link formation in nasal epithelium (rats, monkeys), and similar exposure-response relationships for rat tumors (Casanova et al. 1991, 1994, USEPA 1991a). In both cases, the exposure-response relationships are convex (i.e., nonlinear), and may be explained by a number of mechanisms such as the saturation of formaldehyde metabolic enzymes, decreased removal of formaldehyde by the mucociliary ladder, the saturation of protein-binding kinetic mechanisms, and the saturation of DNA-protein cross-link repair mechanisms (ATSDR 1999). However, at similar formaldehyde concentrations, DNA-protein cross-links in the upper respiratory tract (middle turbinates, lateral wall and septum, nasopharynx) of monkeys are approximately an order of magnitude less than in the nasal cavity of rats (Liteplo and Meek 2003, Casanova and Heck 1991, Health Canada 2001).

The genotoxic effects of formaldehyde appear to be amplified by cell proliferation, which is increased considerably at concentrations greater than 6 ppm and increases the occurrence of malignant lesions in the nasal passages of rats (IARC 2006a). DNA replication has to occur to covert a DNA adduct or cross-link into a mutation, and formaldehyde-induced cytotoxicity/cell proliferation increases the number of DNA replications and the probability that a DNA-protein cross-link will result in mutation before DNA repair can occur. *Both regenerative cell regeneration and DNA-protein cross-links are considered necessary, but not sufficient, events for formaldehyde-induced tumor formation. Cell proliferation appears to be essential for mutations in the development of formaldehyde-induced tumors since there appears to be a more direct relationship between regenerative cell proliferation and tumor formation than for DNA-protein cross-links (CIIT 1999). This is contrary to a mutagenic MOA, where mutation is the first step which initiates a cascade of other key events such as cytotoxicity or cell proliferation (USEPA 2007).*

The International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) has published a framework for analyzing the relevance of a cancer MOA for humans (Boobis et al. 2006). Utilizing that framework, McGregor et al. (2006) indicates that while a role for mutagenicity in the development of formaldehyde-induced tumors cannot be ruled out, an MOA of nonlinear prolonged regenerative cell proliferation due to sustained cytotoxicity (i.e., non-mutagenic MOA) is consistent with biological plausibility and available data. The German MAK Commission concluded that genotoxicity plays no part, or at most a minor part, in formaldehyde's carcinogenicity (MAK 2002). Increased cellular proliferation as a consequence of epithelial cytotoxicity appears to be the most significant determinant of formaldehyde-induced neoplastic progression (Liteplo and Meek 2003, Health Canada 2001). *Therefore, based on available data, exposure to formaldehyde at levels which induce cytotoxicity and sustained regenerative epithelial proliferation in the respiratory tract is considered to represent a carcinogenic hazard to humans based on a nonlinear MOA (Liteplo and Meek 2003, Arts et al. 2006a, NICNAS 2006, Health Canada 2001).*

4.2.2.2.3 WOE for Carcinogenic MOA

The hypothesized MOA for formaldehyde-induced nasal tumors is consistent with the substantial scientific data available and the growing body of evidence supporting the biological plausibility of prolonged regenerative cell proliferation being a causal mechanism in carcinogenesis (Liteplo and Meek 2003, IPCS 2002, Health Canada 2001). Numerous potentially carcinogenic biological activities are associated with the hyperproliferative state (Butterworth et al. 1995). As mentioned previously, formaldehyde-induced cytotoxicity and subsequent regenerative cell proliferation increases DNA replications and the probability that a DNA-protein cross-link will result in a DNA replicating error and mutation. This MOA satisfies several criteria for WOE, including consistency, concordance with exposure-response relationships for intermediate endpoints, biological plausibility, and coherence of the database, and is likely relevant to humans (Liteplo and Meek 2003, NICNAS 2006, Health Canada 2001). See the referenced studies for a more detailed discussion. In regard to target tissues for potential carcinogenic effects, formaldehyde-induced tumors at the site of contact are consistent with biological plausibility and toxicokinetic considerations as formaldehyde is highly water soluble and reactive, and is quickly absorbed (and metabolized) at the site of contact.

4.2.3 Approaches for Evaluation of Carcinogenic Potential

The purpose of the carcinogenic evaluation is to develop a health-protective air concentration consistent with TCEQ guidelines (TCEQ 2006). When the carcinogenic MOA supports a linear dose-response extrapolation (e.g., purely mutagenic MOA) or sufficient information on the carcinogenic MOA is lacking (e.g., likely MOA not understood), the calculation of a health-protective air concentration based on carcinogenic effects due to inhalation is accomplished through use of linear low-dose extrapolation (USEPA default method) and calculation of the resulting URF. The URF can then be used to calculate an air concentration (assuming lifetime exposure) corresponding to a particular target excess risk level. In accordance with TCEQ guidance, TS uses a target excess cancer risk of 1 in 100,000 (TCEQ 2006). However, information on the carcinogenic MOA indicative of nonlinearity (e.g., vinyl acetate and chloroform cytotoxicity) may support approaches other than linear low-dose extrapolation as more appropriate. In such cases, protection against noncancer threshold effects which data indicate are key precursor events in the development of tumors (e.g., formaldehyde-induced cytotoxicity and regenerative cell proliferation) can be considered protective against an increased risk of cancer (TCEQ 2006).

Information on the carcinogenic MOA for formaldehyde supports use of nonlinear approaches as more appropriate than linear approaches for calculation of an air concentration protective of carcinogenic effects (i.e., respiratory/nasopharyngeal cancer). Based on the carcinogenic MOA analysis (see Section 4.2.2), cytotoxicity is believed to be a key precursor event in formaldehyde-induced carcinogenesis and a threshold effect (Schlosser et al. 2003). Additionally, the dose-response relationships for formaldehyde-induced tumors, cell proliferation, and DNA-protein cross-links are highly nonlinear.

Therefore, based on information regarding the carcinogenic MOA, TS believes that a nonlinear BMD analysis based on cellular proliferation (an early key precursor event), or the biologically-based model discussed in CIIT (1999) and Conolly et al. (2004), is more appropriate for

formaldehyde. The nonlinear BMD analysis based on cellular proliferation is presented first as it is the basis of the carcinogenic nonlinear ReV and $^{chronic}ESL_{nonlinear(c)}$, and is followed by a discussion of the CIIT biologically-based model approach. For the sake of comparison and in the interest of making the most informed decision based on scientific merit, linear low-dose extrapolation approaches are also presented.

4.2.3.1 Nonlinear BMD Approach

Since the carcinogenic MOA supports a nonlinear carcinogenic evaluation (see Section 4.2.2), a POD based on a precursor key event (i.e., cellular proliferation) in the development of tumors was determined and appropriate UFs were applied to derive a chronic carcinogenic ReV, which is multiplied by 0.3 to derive the $^{chronic}ESL_{nonlinear(c)}$. The POD is generally the NOAEL, LOAEL, or lower confidence limit on the BMCL (TCEQ 2006).

4.2.3.1.1 BMC/POD

Schlosser et al. (2003) used BMC modeling to calculate BMCs/PODs for rats based on both tumor and cell proliferation endpoints. Tumorigenesis is the primary endpoint of interest in the carcinogenic assessment for development of a POD. Cell proliferation is utilized as an endpoint for POD development because it is believed to play a key role in formaldehyde-induced carcinogenesis, there is a good correlation between elevations in cell proliferation and elevations in tumor risk, and it is predicted by BMC modeling to occur at concentrations lower than those predicted to produce a tumor response. The BMCs/PODs developed in Schlosser et al. (2003) for tumorigenesis and cell proliferation in rats were extrapolated to humans using two mechanistic models. The first model used computational fluid dynamics (CFD) to calculate rates of delivery (flux) of formaldehyde to the nasal lining of rats and humans (direct air flow extrapolation), and human exposure concentrations that produce fluxes equal to those in the rat when the rat is exposed to the BMC(L)s. The second mechanistic model combined CFD with a pharmacokinetic model to calculate tissue dose and formaldehyde-induced DNA-protein cross-links (DPX) as the dose metric (flux-DPX extrapolation), and human exposure concentrations that produce DPX levels equal to those in the rat when the rat is exposed to the BMC(L)s. While the two methods each have their own strengths, TS selected flux-DPX as the basis for interspecies extrapolation (rats to humans) for purposes of developing a chronic carcinogenic ReV since formaldehyde-induced tissue DPX (internal dose metric) is closely associated with tumors (i.e., dose-response, anatomical locations), and may serve as a marker for genotoxicity and play a role in carcinogenesis. USEPA also used DPX as the dose metric for their 1991 carcinogenic assessment (USEPA 1991). This selection has little consequence as the two extrapolation methods result in nearly identical human environmental exposure BMCs/PODs.

Table V of Schlosser et al. (2003) presents BMCs and 95% BMCLs associated with various response rates (1, 5, and 10% response) and models (e.g., multi-stage, Weibull, power law) for both tumor and cell proliferation endpoints in rats. The tumor data modeled included a total of 482 rats exposed at five different concentrations (0.7, 2.0, 6.0, 10.0, and 15.0 ppm) and 122 controls from Kerns et al. (1983) and Monticello et al. (1996) (see Table I of Schlosser et al. 2003). Ninety-four animals that had not been examined for the Monticello et al. (1996) study were included in the modeled tumor data. The modeled cell proliferation data included a total of 236 rats exposed to the same five concentrations (0.7, 2.0, 6.0, 10.0, and 15.0 ppm) and 48

controls from Monticello et al. (1996) (see Table II of Schlosser et al. 2003). Table VIII of Schlosser et al. (2003) presents BMCs and 95% BMCLs associated with various tumor response rates and models, assuming continuous environmental exposure, for both tumor and cell proliferation endpoints based on flux-DPX extrapolation to humans.

BMCLs to be used as PODs should be in or near the range of data where the response is observed (i.e., the lowest dose level supported by the data) to decrease uncertainty (TCEQ 2006). While a BMCL corresponding to a 10% tumor response ($BMCL_{10}$) may be an appropriate standard POD for many chemicals, for formaldehyde, a BMCL corresponding to a 1% tumor response ($BMCL_{01}$) is appropriate as a POD because tumors were observed at exposure levels which produced tumors in 1-5% of the animals in two bioassays. A $BMCL_{01}$ is more conservative than a $BMCL_{10}$ for use as a POD as it corresponds to a lower air concentration (see Table VIII of Schlosser et al. 2003). Additionally, use of cell proliferation as the endpoint, *in lieu* of tumors as the endpoint, is more conservative as cell proliferation is a key event predicted to precede the formation of tumors. TS conservatively selected the 95% $BMCL_{01}$ based on cell proliferation (1% increase in ULLI) and the power law model (0.44 ppm) from Table VIII of Schlosser et al. (2003) for use as the POD_{HEC}. This 95% $BMCL_{01}$ (0.44 ppm) is slightly more conservative than the same 95% $BMCL_{01}$ based on direct air flow extrapolation adjusted to environmental exposure (2.55 ppm from Table VI of Schlosser et al. 2003 divided by a duration adjustment factor of 5.6 cited in study = 0.46 ppm). This POD_{HEC} is based on a threshold endpoint (cell proliferation/cytotoxicity) which is predicted to precede tumor formation (the lowest 95% $BMCL_{01}$ for tumors is 0.71 ppm), and is the lowest of the BMCLs presented based on flux-DPX extrapolation.

4.2.3.1.2 UFs and the Health-Based Chronic ReV and $^{chronic}ESL_{nonlinear(c)}$

The following UFs were applied to the POD_{HEC} of 0.44 ppm: a LOAEL-to-NOAEL UF of 1 (UF_L) was used consistent with TCEQ guidelines (TCEQ 2006) since BMD modeling was performed; an interspecies UF of 3 (UF_A) as interspecies differences in toxicokinetics have already been taken into account by the pharmacokinetic modeling; an intrahuman variability UF of 10 (UF_H) to account for potentially sensitive subpopulations; and a database UF of 1 (UF_D) as the formaldehyde database is extensive (total UF = 30).

$$\text{chronic carcinogenic ReV} = POD_{HEC} / (UF_L \times UF_A \times UF_H \times UF_D)$$
$$= 0.44 \text{ ppm} / (1 \times 3 \times 10 \times 1)$$
$$= 0.44 \text{ ppm} / 30 = 0.0146 \text{ ppm} = 14.6 \text{ ppb}$$

Rounding to two significant figures yields a chronic carcinogenic ReV of 15 ppb (18 $\mu g/m^3$). The chronic carcinogenic ReV is conservatively based on increased cell proliferation, a precursor to tumorigenesis. At the target hazard quotient of 0.3, the $^{chronic}ESL_{nonlinear(c)}$ is 4.5 ppb (5.5 $\mu g/m^3$) (Table 6).

Parameter	Summary
Study	Schlosser et al. (2003)

Study Population	total of 236 exposed rats, 48 controls
Study Quality	high
Exposure Levels	0.7, 2.0, 6.0, 10.0, and 15.0 ppm
Exposure Duration	2-year study (with interim sacrifices at 3, 6, 12, and 18 months)
Critical Effects	cell proliferation (key precursor event to tumorigenesis)
POD_{HEC} ($BMCL_{01}$)	0.44 ppm (already adjusted for continuous environmental exposure)
Total UFs	30
Interspecies UF	*3*
Intraspecies UF	*10*
LOAEL-to-NOAEL UF	*1*
Subchronic to chronic UF	*NA*
Incomplete Database UF	*1*
Database Quality	*high*
Chronic Carc. ReV (HQ = 1)	**18 µg/m^3 (15 ppb)**
$^{chronic}ESL_{nonlinear(c)}$ (HQ = 0.3)	**5.5 µg/m^3 (4.5 ppb)**

Table 6 Derivation of the Chronic Carcinogenic ReV and $^{chronic}ESL_{nonlinear(c)}$

4.2.3.2 CIIT Full Biologically-Based Model

CIIT incorporated available mechanistic and dosimetric information on formaldehyde to develop a risk assessment consistent with USEPA guidelines for carcinogenic risk assessment (CIIT 1999). Although CIIT primarily developed the model (CIIT 1999), other entities involved were USEPA, Health Canada, and Toxicology Excellence for Risk Assessment (*TERA*), as well as those involved in the external peer review (Liteplo and Meek 2003). CIIT is now the flagship institute of the Hamner Institutes of Health Sciences.

4.2.3.2.1 Model Description

The goal of CIIT (1999) was to develop a dose-response model for formaldehyde which incorporates as much of the biological database on formaldehyde as possible. The CIIT model is an example of how relevant biological and mechanistic information can replace default assumptions (e.g., linear dose-response relationship) in the estimation of human respiratory tract risk, offering the potential to decrease the risk assessment uncertainties associated with interspecies and high-to-low dose extrapolations by maximizing the use of scientific data (NICNAS 2006, CIIT 1999).

Appropriate dosimetry is critical in interspecies extrapolation because of differences between test species (e.g., rats) and humans in the anatomy of nasal/respiratory passages, air flow patterns, and breathing patterns (obligate nasal versus oronasal) (NICNAS 2006). For example, in humans

(oronasal breathers), effects are likely to be observed deeper within the respiratory tract (similar to formaldehyde-exposed monkeys). Species differences in nasal dosimetry are accounted for in CIIT (1999) by anatomically realistic three-dimensional computational fluid dynamics (CFD) modeling of formaldehyde flux in various rat and human nasal regions (Liteplo and Meek 2003). Additionally, the model accounts for oronasal breathing in humans and incorporates local doses (surface fluxes) over the entire human respiratory tract (see Section 6.3 of CIIT 1999). The upper respiratory tract was considered to begin at the lips or nostrils, through the oropharyx, continuing to the proximal end of the trachea (beginning of the lower respiratory tract). The lower respiratory tract is divided into the tracheobronchial and pulmonary regions. The tracheobronchial region consists of the trachea, bronchi, and bronchioles, ending at the terminal bronchioles after 9 to 22 branching generations. The pulmonary (gas-exchange) region follows the terminal bronchioles, beginning with respiratory bronchioles which eventually branch into alveolar sacs. Regional dose is a function of factors affecting the amount delivered by inhaled air (e.g., airflow patterns, air-phase diffusion) and the absorption characteristics of the lining (e.g., amount absorbed at the air-lining interface, mucous/tissue-phase diffusion, clearance rates, chemical reactions and solubility) within various regions of the respiratory tract (NICNAS 2006, CIIT 1999). Species differences in these factors determine species-specific regional dose distributions. The model utilizes anatomically realistic models to accurately describe the effects of interspecies anatomical differences on the respiratory tract dosimetry of formaldehyde (CIIT 1999).

CFD-generated predictions of regional flux (dose) and number of cells at risk are linked to two MOAs which jointly contribute to tumor formation in the CIIT model: cytotoxicity/regenerative cell proliferation and mutagenicity (mediated by DNA-protein cross-links) (Conolly et al. 2003). The model incorporates regenerative cell proliferation as a required step in tumor induction and a contribution from mutagenicity that has the greatest impact at low exposures through modeling of complex functional relationships for cancer due to the effects of formaldehyde on mutation, cell replication, and exponential clonal expansion (Liteplo and Meek 2003). Formaldehyde is assumed to act as a direct mutagen in the model (proportional to tissue DNA-protein cross-link concentration) despite animal studies which suggest a threshold for carcinogenic effects, which provides a conservative and cautionary element in recognition of a lack of a fully elucidated carcinogenic MOA (NICNAS 2006). The CIIT model incorporates data on cell proliferation and the probability of mutation (based on tissue DNA-protein cross-link data) into a two-stage clonal growth model, which describes cancer as a succession of genetic changes and altered growth behaviors that lead to the progressive conversion of normal cells into cancer cells (Conolly et al. 2003). The clonal growth model structure is identical to other biologically-based, two-stage clonal growth models (a.k.a. Moolgavkar, Venzon, and Knudson (MVK) models) and incorporates information on normal growth, cell cycle time, and respiratory tract region-specific cells at risk. The incorporation of roles for both cytotoxicity and mutagenicity represents a significant advance over previous risk assessments. The clonal growth model provides a good description of the relatively high dose rat tumor data, describes a low-dose linear response for both rats and humans at exposure levels where cytotoxicity and regenerative cell proliferation do not play a role in carcinogenesis, and was developed to be conservative. Where scientific uncertainty existed, choices were made that tended to overpredict risk (CIIT 1999).

Induction of a proliferative response in response to cytotoxicity plays a critical role in carcinogenesis of many compounds which are also mutagenic, and two-stage cancer modeling

has been used for formaldehyde to reflect the relative importance of cytotoxicity-induced cell proliferation versus chemically-induced direct mutation in tumorigenesis (Subramaniam et al. 2007). *A sensitivity analysis of the CIIT model indicates that direct mutation is not a significant action of formaldehyde as the optimum value for the KMU parameter, which determines the extent of direct mutation, is zero (Conolly et al. 2004, CIIT 1999).* In other words, the model explains tumor data optimally without dependence on a directly mutagenic effect of formaldehyde (i.e., when KMU is zero thereby excluding a direct mutagenic effect) (Conolly et al. 2003).

4.2.3.2.2 CIIT Model Calculation of Air Concentrations at 1 in 100,000 Excess Cancer Risk

Since the CIIT model is not linear, the CIIT model itself must be used to calculate an air concentration at 1 in 100,000 excess cancer risk. Pursuant to a TCEQ request, CIIT performed modeling assuming lifetime environmental exposure for smokers, nonsmokers, and smokers/nonsmokers mixed utilizing the published CIIT hockey-stick model from Conolly et al. (2004), the TCEQ target excess cancer risk level of 1 in 100,000, and the TCEQ default lifetime exposure duration of 70 years. The CIIT hockey-stick model is much more conservative than the alternative J-shaped dose-response model as the response at low doses is forced to be linear, reflecting the linearity of the DNA-protein cross-link model (contribution of mutagenicity) over the low environmental concentration range. CIIT modeling performed for the TCEQ indicates that the lifetime environmental air concentrations corresponding to an additional cancer risk level of 1 in 100,000 for smokers, nonsmokers, and smokers/nonsmokers mixed are 300, 955, and 400 ppb, respectively. Dr. Cecilia Tan of CIIT provided a discussion of the modeling results that is provided in Appendix B. *Given the potential inherent sensitivity of the model, use of the most conservative air concentration corresponding to 1 in 100,000 additional cancer risk (300 ppb for smokers) is justified for evaluation for potential use in developing a carcinogenic-based chronic ESL.*

A recent paper by Subramaniam et al. (2007) indicates that the dose-response predictions by the CIIT model at concentrations less than those causing tumors in rats are sensitive to the choice of control data. Although the work is not yet published, information in a presentation by the same group of researchers at the 2006 Society for Risk Analysis (SRA) conference indicates that using National Toxicology Program (NTP) inhalation controls, human risks from the hockey stick model can be 60 times higher using their re-implementation of the model at 10 ppb (see slides 9 and 21 in Appendix C). While the scientific merit or defensibility of altering the model control data is debatable, even considering an uncertainty factor of 60, the noncarcinogenic ESL (2.7 ppb) would be lower than the most conservative carcinogenic ESL based on the CIIT model (300 ppb) divided by 60 (5 ppb). *Therefore, TS believes the results of the CIIT model (300 ppb) demonstrate that air concentrations protective of noncarcinogenic irritant effects (chronic noncarcinogenic ReV of 8.9 ppb and* $^{chronic}ESL_{nonlinear(nc)}$ *of 2.7 ppb) are also protective of carcinogenic effects.* This is consistent with Health Canada (2001), which concluded that, "output of the model is considered adequate as a basis to ensure that measures taken to prevent sensory irritation in human populations are sufficiently protective with respect to carcinogenic potential."

4.2.3.2.3 Evaluating Susceptibility from Early-Life Exposures

USEPA (2005b) provides default age-dependent adjustment factors (ADAFs) to apply to the URF to account for potential increased susceptibility in children due to early-life exposure when a chemical has clearly been shown by the scientific community to act through a mutagenic MOA for carcinogenesis (as opposed to unknown or multiple MOAs). The scientific community has not shown the carcinogenic MOA for formaldehyde to be mutagenic. While the weight-of-evidence indicates that formaldehyde is capable of reacting with DNA and producing genotoxic effects, especially at high concentrations when metabolic capacities are exceeded (ATSDR 1999), it is only weakly genotoxic (Liteplo and Meek 2003). Additionally, although DNA-protein cross-links play a role in the generation of mutations, there seems to be a more direct relationship between regenerative cell regeneration and tumor formation than between DNA-protein cross-links and tumor formation (CIIT 1999, Liteplo and Meek 2003). There was evidence of cytotoxicity in all cancer cases in the Swenberg et al. (1983) rat experiments, and cytotoxicity leading to cell necrosis and rapid replication is a known cause of cancer (Imbus 1988). Biologically-based modeling of the carcinogenic response indicates that direct mutation is not a significant action of formaldehyde (i.e., the optimum value for KMU, which determines the extent of direct mutation, is zero) (Conolly et al. 2004, CIIT 1999).

The most significant determinant of formaldehyde-induced neoplastic progression appears to be increased cellular proliferation as a consequence of epithelial cytotoxicity. Cytotoxicity followed by regenerative cell proliferation is a nongenotoxic MOA (Butterworth et al. 1995). Animal data suggest formaldehyde is an epigenetic carcinogen (as opposed to having a mutagenic MOA), implying a threshold below which there is no carcinogenic response (Edling et al. 1988). Formaldehyde appears to be an example of a chemical with an MOA which contains one component with a nonlinear dose-response (cytotoxicity/cell proliferation) and one which may be assumed to be low-dose linear (DNA-protein cross-links/mutagenicity), resulting in a nonlinear dose-response for tumor incidence (Rhomberg et al. 2007).

As previously mentioned, utilizing the IPCS framework (Boobis et al. 2006) for analyzing the relevance of a cancer MOA for humans, McGregor et al. (2006) indicate that although a role for mutagenicity in the development of formaldehyde-induced tumors cannot be ruled out, an MOA of nonlinear prolonged regenerative cell proliferation due to sustained cytotoxicity (i.e., non-mutagenic MOA) is consistent with biological plausibility and available data. Additionally, the German MAK Commission concluded that genotoxicity plays no part, or at most a minor part, in formaldehyde's carcinogenicity (MAK 2002). Therefore, based on available information and consistent with USEPA (2005b) and TCEQ (2006) guidelines, ADAFs would not be applied if a $^{chronic}ESL_{nonlinear(c)}$ based on the CIIT model (or a $^{chronic}ESL_{linear(c)}$) were to be selected by TS. Regardless, the issue is without consequence since even if ADAFs were applied to the $^{chronic}ESL_{nonlinear(c)}$ based on the CIIT model, the resulting value (300 ppb x 0.6 = 180 ppb) would be significantly higher than the chronic noncarcinogenic ReV (8.9 ppb) and $^{chronic}ESL_{nonlinear(nc)}$ (2.7 ppb).

4.2.3.2.4 Use of CIIT Model by Other Environmental Agencies

USEPA

For their 2006 NATA of 1999 emissions data (a.k.a. the 1999 NATA) and the 2004 *Combustion Turbine Source Category Risk Characterization*, USEPA judged CIIT (1999) to represent the

best application of available mechanistic and dosimetric science on dose-response (i.e., it incorporates state-of-the-art analyses for species-specific dosimetry) and the best available approach for portal-of-entry cancers due to formaldehyde (USEPA 2006, 2004). Therefore, USEPA utilized a URF for formaldehyde of 5.5E-09 per µg/m^3 (6.8E-09 per ppb or 6.8E-06 per ppm) based on CIIT (1999) for the 1999 NATA (NATA at EPA). The 1999 NATA URF indicates that formaldehyde is about 2,450 times less potent of a carcinogen than the 1991 URF currently on IRIS, which is based on a rat study without consideration of relevant biological and mechanistic information. Derivation of the URF is documented in Appendix H of USEPA's *Combustion Turbine Source Category Risk Characterization* (USEPA 2004) (see Appendix D).

Examination of predicted risks at various environmental exposure levels based on CIIT (1999) indicates that use of the 1999 NATA URF (5.5E-09 per µg/m^3 or 6.8E-09 per ppb) to evaluate long-term levels less than 100 ppb, where long-term environmental levels (< 10 ppb) are expected, may be conservative (i.e., yields higher risk estimates than those predicted for lower concentrations such as 1-20 ppb) (see Table 7-1 of CIIT 1999). However, predicted risks increased somewhat based on the updated CIIT model (hockey-stick model for cytotoxicity-regenerative cell proliferation in Conolly et al. 2004), making use of the 1999 NATA URF under-predictive for smokers and smokers/nonsmokers mixed at environmentally-relevant exposure levels (1-20 ppb), while still being conservative for nonsmokers (see Table 8 of Conolly et al. 2004).

Health Canada and Australia

In addition to USEPA having utilized the CIIT model, Health Canada indicates in their *Priority Substances List Assessment Report* for formaldehyde (Health Canada 2001) that the CIIT model is considered to provide the most defensible estimates of cancer risk and is clearly preferred for characterization of the dose-response for formaldehyde-induced cancer on the basis that it encompasses more of the available biological data, thereby offering considerable improvement over default approaches.

Australia's DHA also considers the CIIT model to give more reliable estimates of cancer risk than default assumptions due to the incorporation of all available biological data (NICNAS 2006).

Based on CIIT modeling results, Health Canada concluded that cancer risk (upper respiratory tract) associated with formaldehyde in air in Canada is exceedingly low (risk < 2.7E-08). Australia's DHA drew similar risk conclusions for the general population (including children) due to ambient air levels in Australia (maximum annual average of 5.5 ppb) based on the CIIT model. The long-term (1 month to 1 year) mean ambient air concentrations reported in Section 2.3.2.1.1 of Health Canada (2001) (0.78 to 8.76 µg/m^3 or 0.63 to 7.1 ppb) are similar to or greater than sampling site means measured in Texas from 1997-2007 (1.5 to 5.2 ppb with a statewide mean of 3.6 ppb), and in the US in 2006 (mean of 3.1 ppb, median of 2.1 ppb). Based on the low cancer risks predicted using the CIIT (1999) model for formaldehyde in Canadian air, Health Canada places emphasis for the characterization of formaldehyde health risk on the noncarcinogenic effects that occur at the lowest concentrations (i.e., sensory irritation) (Health Canada 2001). *Liteplo and Meek (2003), who are with Health Canada, concluded that, "output of the model is considered adequate as a basis to ensure that measures taken to prevent sensory*

irritation in human populations are sufficiently protective with respect to carcinogenic potential." TS concurs with this conclusion and notes that the chronic noncarcinogenic ReV (8.9 ppb) and $^{chronic}ESL_{nonlinear(nc)}$ (2.7 ppb) and lower than the chronic carcinogenic ReV (15 ppb) and $^{chronic}ESL_{nonlinear(c)}$ (4.5 ppb) and the most conservative value from the CIIT model (300 ppb).

4.2.3.3 Linear Low-Dose Extrapolation Approaches

These results are presented for comparison purposes only as TS does not believe that linear low-dose extrapolation is the most appropriate method for evaluating the carcinogenic potential of formaldehyde. Linear extrapolation likely over-predicts risk at low (e.g., environmentally-relevant) exposure levels because: (1) the dose-response relationships for both tumor and cell proliferation endpoints are highly nonlinear; (2) cytotoxicity is believed to play a key role in formaldehyde-induced carcinogenesis and is a threshold effect; and (3) a stronger association between formaldehyde exposure and nasal cancers may be expected in epidemiology studies if true cancer risk were similar to that predicted utilizing linear low-dose extrapolation (Schlosser et al. 2003). *Therefore, TS believes the nonlinear BMD approach discussed in Section 4.2.3.1 to be most appropriate for assessing human health risk (as opposed to linear low-dose extrapolation).*

4.2.3.3.1 Linear BMD Approach

As previously discussed, Schlosser et al. (2003) utilized a BMD approach to evaluate the carcinogenicity of formaldehyde, as opposed to the full biologically-based modeling approach employed in CIIT (1999) and Conolly et al. (2004). The approach combined BMD and pharmacokinetic modeling to: (1) calculate human BMCs for use in a margin-of-exposure (MOE) analysis (e.g., environmental exposure human BMCs in Table VIII and MOEs in Table IX of Schlosser et al. 2003), which is a nonlinear approach; and (2) estimate human cancer risk from formaldehyde exposure assuming low-dose linearity (see risk estimates in Table IX of Schlosser et al. 2003). Schlosser et al. (2003) stated that if a BMD method is preferred over the CIIT model (CIIT 1999, Conolly et al. 2004), a nonlinear approach is believed to be more appropriate than the low-dose linearity approach, although BMD results based on low-dose linearity were presented for comparison. A nonlinear BMD approach was discussed in Section 4.2.3.1 above, and a BMD approach based on linear low-dose extrapolation is presented below.

4.2.3.3.1.1 Determination of URFs and 1 in 100,000 Excess Cancer Risk

The two mechanistic models for extrapolation to humans (direct air flow and flux-DPX) gave identical results when used to estimate human cancer risk assuming linear low-dose extrapolation for tumors (see Table IX of Schlosser et al. 2003). Using flux-DPX or direct air flow extrapolation, formaldehyde-induced tumors as the endpoint of interest (as opposed to cell proliferation), and assuming no threshold (low-dose linearity), the human additional lifetime cancer risks given in Table IX of Schlosser et al. (2003) at 0.1 ppm for the 95% upper bound and maximum likelihood estimate (MLE) are 1.4E-03 and 1.3E-03, respectively. These risk estimates for the 95% upper bound and MLE correspond to URFs of 1.4E-05 and 1.3E-05 per ppb, respectively (e.g., 95% upper bound URF = 1.4E-03 / 100 ppb = 1.4E-05 per ppb). Air concentrations corresponding to an additional lifetime cancer risk of 1 in 100,000 using the 95% upper bound and MLE URFs would be approximately 0.7 and 0.8 ppb, respectively:

1 in 100,000 additional lifetime risk air concentration using the 95% upper bound =
target risk level / URF = 1.0E-05 / 1.4E-05 per ppb = 0.71 ppb

1 in 100,000 additional lifetime risk air concentration using the MLE =
target risk level / URF = 1.0E-05 / 1.3E-05 per ppb = 0.77 ppb

For comparison, based on the 1991 USEPA URF (1.6E-05 per ppb), which is slightly more conservative than the URFs mentioned above based on Schlosser et al. (2003), the air concentration at a lifetime cancer risk of 1 in 100,000 is approximately 0.6 ppb:

1 in 100,000 additional lifetime risk air concentration using the USEPA URF =
target risk level / URF = 1.0E-05 / 1.6E-05 per ppb = 0.625 ppb

However, USEPA no longer considers the URF (1.3E-05 per $\mu g/m^3$ or 1.6E-05 per ppb) on IRIS, which utilized a 1983 rat study (Kerns et al. 1983b) and was placed on IRIS in 1991, to be based on the best available science (USEPA 2006, 2004). USEPA is in the process of updating the IRIS assessment and awaiting updated epidemiological studies from NCI. The draft IRIS reassessment is currently scheduled to be out for public comment in April 2008, with the final assessment posted in January 2009.

4.2.3.3.2 Linear Approach Based on Human Nasopharyngeal Cancer Relative Risk

As a relatively crude comparison to the URFs mentioned above based on Schlosser et al. (2003) and that from USEPA, TS calculated a URF and the 1 in 100,000 air concentration based on the relative risk for nasopharyngeal cancer reported for the highest cumulative exposure group in Table 5 of Hauptmann et al. (2004), the last published NCI cohort update. TS employed various conservative assumptions. The URF calculation methodology is one employed in USEPA (1986). More specifically, TS used the relative risk model equation found on various pages of that document (e.g., bottom of page 8-209, top of page 8-215), which is a linear low-dose extrapolation method. The equation is given below and requires estimates of background rate for the cancer of interest, relative risk from the study, and average lifetime exposure concentration for the exposure group of interest (i.e., the exposure group corresponding to the relative risk utilized).

TS utilized readily available conservative values for these parameters so that the resulting URF and air concentration values could be conservatively compared to the URFs from the linear BMD and IRIS assessments above. The highest cumulative exposure group in Hauptmann et al. (2004) had a high relative risk for nasopharyngeal cancer (4.14) compared to other exposure groups and metrics. The highest cumulative exposure group was $\geq$ 5.5 ppm-years, and the low end was used (5,500 ppb-years) as it was readily available and the most conservative for this exposure group (i.e., results in a more conservative URF).

The value of 5,500 ppb-years corresponds to an average lifetime environmental exposure concentration of 18.7 ppb (5,500 ppb-years x (5/7 days) x (8/24 h) x (1/70 years) = 18.7 ppb). This is a very conservative value as it is based on a cumulative exposure metric which includes a 15-year lag and assumes no exposure outside of work. Average indoor exposure to formaldehyde is significant relative to the 18.7 ppb calculated above, and may exceed it based on available

data. Most workers were ≤ 30 years old at the beginning of the cohort (see Table 1 of Hauptmann et al. 2004), and most were followed for over 30 years. As the background nasopharyngeal cancer rate, TS used the US nasopharyngeal cancer mortality rate of 0.8 per 100,000 for ages over 65 years old (Table XX-4b of SEER 2007b) as it may be the most appropriate readily available background rate and results in a more conservative URF (i.e., it is 8 times the rate for ages less than 65 years old and 4 times the rate for white males, which comprised most of the cohort). These values were used with the following equation (USEPA 1986):

$$\text{URF} = \text{background mortality rate for the cancer endpoint} \times \frac{\text{(relative risk -1)}}{\text{average lifetime exposure level}}$$

URF = 0.8E-05 x ((4.14 -1)/18.7 ppb) = 1.3E-06 per ppb

1 in 100,000 additional lifetime risk air concentration =
target risk level / URF = 1.0E-05 / 1.3E-06 per ppb = 7.7 ppb

This same methodology was used with the nasopharyngeal cancer relative risk (1.19) reported for the next highest cumulative exposure group (1.5 < 5.5 ppm-years) in Table 5 of Hauptmann et al. (2004), along with the lower (1,500 ppb-years) and upper (5,500 ppb-years) ends of the cumulative exposure range. This resulted in a URF range of 8.1E-08 to 3.0E-07 per ppb, and an air concentration range at 1 in 100,000 cancer risk of 33 to 123 ppb (calculations not shown).

While relatively crude in nature, these three examples demonstrate that employing even very conservative parameter values, the URFs resulting from this method (8.1E-08 to 1.3E-06 per ppb) based on relative risks from the NCI epidemiological study (Hauptmann et al. 2004) are about one or two orders of magnitude less conservative than the URF based on animal data currently on IRIS (1.6E-05 per ppb) or those based on the linear BMD analysis (1.3E-05 to 1.4E-05 per ppb). Additionally, the chronic ESL based on noncarcinogenic effects (2.7 ppb) is lower than the air concentrations corresponding to 1 in 100,000 cancer risk (7.7-123 ppb) based on the URFs resulting from this method.

As an additional comparison to the 1 in 100,000 air concentration using the USEPA URF and the linearized multi-stage model (0.6 ppb), Imbus (1998) presents MLE estimates for other models (e.g., probit, multi-hit). The MLE air concentrations from Imbus (1988) corresponding to 1 in 100,000 excess risk are several orders of magnitude higher, ranging from 170-2,140 ppb.

Again, as TS does not believe that linear low-dose extrapolation is the most appropriate method for evaluating the carcinogenic potential of formaldehyde, these results are presented for comparison purposes only.

4.2.4 Discussion of Potential Carcinogenic-Based ESLs

Utilization of the different approaches for evaluating the carcinogenic potential of formaldehyde resulted in the following values:

- 4.5 ppb (5.5 µg/m^3) based on a nonlinear BMD approach for a key precursor event (cell

proliferation) predicted to precede tumorigenesis

- 300 ppb (369 µg/m^3) based on the most conservative 1 in 100,000 additional lifetime risk level (for smokers) from the CIIT full biologically-based model
- 0.6 to 0.8 ppb (0.7 to 1 µg/m^3) based on a 1 in 100,000 additional lifetime risk level from linear low-dose extrapolation (USEPA default approach) of rat data

For reasons mentioned in Sections 4.2.3.2 and 4.2.3.2.4, TS believes that results from the CIIT full biologically-based model are more likely to be representative of air concentrations corresponding to an additional lifetime cancer risk of 1 in 100,000 than results from linear low-dose extrapolation. *However, considering TCEQ's interest in protecting public health and the potential uncertainty which may be associated with the CIIT model (e.g., ongoing sensitivity analysis by Subramaniam et al.), TS has selected the* $^{chronic}ESL_{nonlinear(c)}$ *of 4.5 ppb as the chronic carcinogenic-based ESL (*$^{chronic}ESL_{nonlinear(c)}$*).*

The $^{chronic}ESL_{nonlinear(c)}$ (4.5 ppb or 5.5 µg/m^3) is expected to be protective of carcinogenic effects because of the following:

- the default linear low-dose extrapolation method does not appear to be appropriate;
- the endpoint (cytotoxicity) is believed to be a key event in formaldehyde-induced carcinogenesis;
- the endpoint is a threshold effect predicted to precede tumor formation; and
- it is significantly lower than what the carcinogenic-based ESL would be (300 ppb) if based on the full biologically-based model, which many researchers consider representative of the best available science.

This $^{chronic}ESL_{nonlinear(c)}$ is based on preventing cytotoxicity, of which there was evidence in all cancer cases in CIIT rat experiments (Swenberg et al. 1983), and which was not increased in the nasal mucosa of rats until approximately 5,600 ppb, the same level where the incidence of nasal cancer began to increase in Kerns et al. (1983) (as cited by Imbus 1988). For the Kerns et al. (1983) and Tobe et al. (1985) studies combined, nasal cancer incidence was zero in 268 rats (most sensitive laboratory animal species) exposed to 2,000 ppb (Imbus 1988). Therefore, the $^{chronic}ESL_{nonlinear(c)}$ (4.5 ppb) is at least 1,200 times less than concentrations shown to cause nasal cancer in rats in the Kerns et al. (1983) study (5,600 and 14,300 ppb), and is about 444 times lower than the nasal cancer NOAEL in this study (2,000 ppb). Kerns et al. (1983) is the basis for the current (1991) USEPA URF on IRIS. Additionally, the $^{chronic}ESL_{nonlinear(c)}$ (4.5 ppb) is significantly lower than the short-term air quality guideline for Europe (81 ppb), a concentration at which WHO (2000) indicates there is negligible risk of upper respiratory tract cancer in humans. If necessary for the protection of public health based on scientific merit, TS will re-evaluate the carcinogenic potential of formaldehyde when the updated NCI studies are published or upon completion of the IRIS reassessment.

The chronic noncarcinogenic ReV/ESL values (8.9 and 2.7 ppb) being lower than the carcinogenic ReV/ESL values (15 and 4.5 ppb) indicates that chronic values which are protective of noncarcinogenic irritant effects are also protective of carcinogenic effects. This is consistent with Health Canada (2001), and others (e.g., Naya and Nakanishi 2005), which conclude that measures taken to prevent sensory irritation in human populations are sufficiently

protective with respect to carcinogenic potential.

4.3. Welfare-Based Chronic ESL

Data on long-term vegetative effects of formaldehyde is limited, but available data indicate that levels protective of irritant effects in humans are also expected to be protective of effects on plants (Cape 2003). For example, exposure to 900 ppb for 14 days has been shown to cause bean leaf margin necrosis (Van Haut and Prinz 1979), and exposure to 365 ppb for 4 weeks affected bean plant leaf weight and appearance, although the authors attributed only a small portion of the observed variation to formaldehyde exposure (Mutters and Madore 1993). A $^{chronic}ESL_{veg}$ was not developed since available data indicate that the levels producing effects are significantly higher than the calculated chronic noncarcinogenic ReV (8.9 ppb) and $^{chronic}ESL_{nonlinear(nc)}$ (2.7 ppb). Therefore, the chronic noncarcinogenic ReV and $^{chronic}ESL_{nonlinear(nc)}$ are expected to be protective of chronic vegetative effects and there is no need to develop a $^{chronic}ESL_{veg}$ value. Additionally, based on historical data, long-term concentrations measured in Texas ambient air (1997-2007 sampling site means of 1.5 to 5.2 ppb, mean across sites of 3.6 ppb) are not expected to approach phytotoxic levels.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

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

- chronic ReV (noncarcinogenic) = 11 µg/m^3 (8.9 ppb)
- $^{chronic}ESL_{nonlinear(nc)}$ = 3.3 µg/m^3 (2.7 ppb)
- chronic ReV (carcinogenic/nonlinear) = 18 µg/m^3 (15 ppb)
- $^{chronic}ESL_{nonlinear(c)}$ = 5.5 µg/m^3 (4.5 ppb)

The noncarcinogenic $^{chronic}ESL_{nonlinear(nc)}$ of 2.7 ppb is lower than the carcinogenic $^{chronic}ESL_{nonlinear(c)}$ of 4.5 ppb. Therefore, the long-term ESL is 2.7 ppb (3.3 µg/m^3) based on noncarcinogenic effects (Table 1). The $^{chronic}ESL_{nonlinear(nc)}$ is only used for air permit reviews, and is not used for the evaluation of ambient air monitoring data. For the evaluation of long-term air monitoring data, the chronic noncarcinogenic ReV of 8.9 ppb (11 µg/m^3) is the lowest chronic comparison value, although the carcinogenic-based chronic ReV may also be used for the evaluation of air data (Table 1).

Chapter 5. References

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Appendix A: Benchmark Dose Modeling Results for Kulle et al. (1987, 1993)

Mild/moderate eye irritation combined was selected as the endpoint of concern from Kulle et al. (1987, 1993). Results from the benchmark dose modeling of data on mild, moderate, and mild/moderate eye irritation combined from Table 3 in Kulle et al. (1993) using USEPA Benchmark Dose Software (Version 1.4.1) are presented below. For modeling mild irritation alone, the number of subjects responding with moderate irritation was subtracted from the total number of subjects as those reporting moderate irritation were not available to report mild. Likewise, for modeling moderate irritation, the number of subjects responding with mild irritation was subtracted from the total number of subjects. For modeling mild/moderate irritation combined, the endpoint of concern, no adjustment to the total number of subjects was necessary. Goodness of fit was evaluated by visual inspection with scaled residuals < 2 and goodness-of-fit p values > 0.1. While several models had an adequate fit for mild/moderate eye irritation combined, the probit and logistic models gave lower (and similar) AIC values, indicating a better fit. Therefore, the benchmark concentrations low (BMCLs) corresponding to the 5% response level ($BMCL_{05}$) from these two models (0.286 and 0.316 ppm) were averaged to give a $BMCL_{05}$ of 0.30 ppm. This value is significantly below the study NOAEL (0.5 ppm) at which 0% of the study participants responded.

Table 7 Kulle et al. Modeled Data

Kulle et al. (1987, 1993) Modeled Data

Exposure Concentration (ppm)	Number of Subjects	Number Responding with Mild Irritation	Number Responding with Moderate Irritation	Number Responding with Mild or Moderate Irritation
0	19	1	0	1
0.5	10	0	0	0
1	19	4	1	5
2	19	6	4	10
3	9	5	4	9

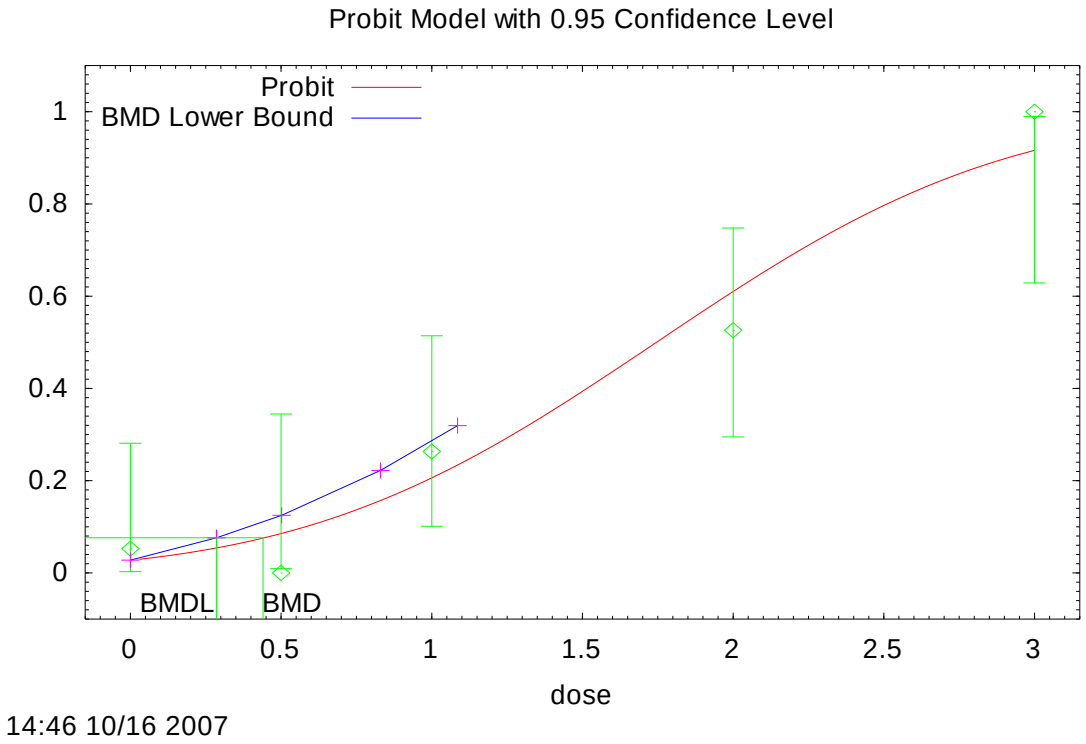
Data from Table 3 of Kulle et al. (1993)

Table 8 BMC Modeling Results based on Kulle et al. (1987, 1993) Data

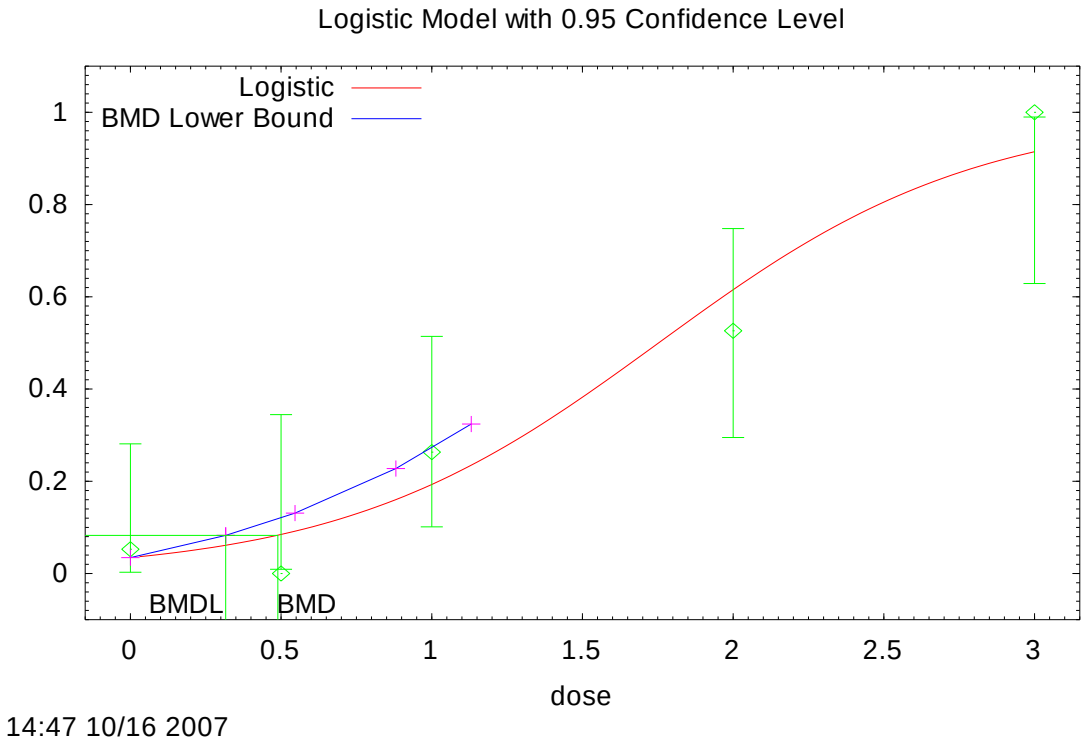
Level of Eye Irritation	BMC_{05} (ppm)	$BMCL_{05}$ (ppm)	Dichotomous Model	Goodness-of-Fit p value [a]	AIC value [b]
mild	0.560	0.363	logistic	0.3710	55.660
mild	0.792	0.321	weibull	0.1974	57.391
mild	0.743	0.305	gamma	0.1790	57.924
mild	0.499	0.326	probit	0.3567	55.795
moderate	1.134	0.652	weibull	0.7010	29.002
moderate	1.068	0.611	gamma	0.5863	30.035
moderate	1.105	0.626	logistic	0.5545	30.190
moderate	1.055	0.637	probit	0.5186	30.532
mild + moderate	0.440	**0.286**	probit	0.3686	64.645
mild + moderate	0.679	0.329	gamma	0.1819	66.839
mild + moderate	0.677	0.320	weibull	0.2108	66.225
mild + moderate	0.489	**0.316**	logistic	0.3644	64.737

[a] p value > 0.1 indicates adequate fit.
[b] lower AIC values generally indicate better fit, and a difference of 2 is often used as a "rule of thumb."

Benchmark Dose Computation: Probit Model for Mild/Moderate Eye Irritation Combined
Specified effect =0.05
Risk Type = extra risk
Confidence level = 0.95
BMD = 0.440167 ppm
BMDL = 0.286019 ppm



Benchmark Dose Computation: Logistic Model for Mild/Moderate Eye Irritation Combined
Specified effect =0.05
Risk Type = extra risk
Confidence level = 0.95
BMD = 0.489256 ppm
BMDL = 0.316306 ppm



Appendix B: CIIT Modeling Results for the TCEQ

The following information was provided by Dr. Cecilia Tan of CIIT regarding the modeling runs performed at the request of TCEQ.

Conolly et al. (2003) developed a biologically motivated computational model to describe the F344 rat squamous cell carcinoma (SCC) data. The overall model consisted of three linked modules: (1) an anatomically realistic three-dimensional computational fluid dynamics (CFD) model described rat nasal airflow and site-specific flux of formaldehyde into the tissue in which the nasal SCC developed; (2) flux was the dose driver for two modes of action: formation of DNA-protein cross-links (DPX) and cytolethality/regenerative cellular proliferation (CRCP); and (3) a two-stage clonal growth model that links modes of action with mutation accumulation and tumor formation. It was found that the tumor dose-response predicted by this model was sensitive to the shape of dose-response for CRCP, which is J-shaped. Besides the J-shaped tumor dose-response, Conolly et al. (2003) also provided a hockey-stick-shaped transformation of the CRCP data to estimate a monotonically increasing tumor dose response.

This model was extended to humans (Conolly et al. 2004) to predict the potential human cancer in response to inhaled formaldehyde. The parameters and their values used for the human model can be found in Table 4 in Conolly et al. (2004). We used this published human model to estimate the inhaled formaldehyde concentrations that could potentially result in a 1 in 100,000 tumor risk level if an individual inhales a constant level of formaldehyde for 70 years. The hockey-stick-shaped CRCP was used to predict tumor responses for non-smokers, a mixed population of non-smokers and smokers, and for smokers. For each group, the model was run repeatedly at various inhaled concentrations until the model simulates a 1 in 100,000 tumor risk. Our results show that for smokers, mixed, and nonsmokers, the inhaled concentrations that result in 1 in 100,000 tumor risk level are 300 ppb, 400 ppb, and 955 ppb, respectively.

Appendix C: Slides from 2006 Society for Risk Analysis (SRA) Conference

Consideration of Uncertainties in the CIIT Model for Formaldehyde Carcinogenicity in the Human Respiratory Tract

Crump KS[1], Subramaniam R[2], White P[2], Chen C[2], Schlosser P[2], Van Landingham C[1], Covington TR[1], DeVoney D[2]

[1]ENVIRON International Corporation,
[2]US EPA

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

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Effect of animal controls upon human risk at constant 0.01 ppm

	95% LB DPX	Point Est DPX	95% UB DPX	Risk/ CIIT Risk	95% UB DPX
	Hockey Stick				**J-Shape**
CIIT Model	---	---	3.2E-07	1	-9.7E-05
Modified model using					
All Historical Controls	0	0	9.2E-07	3	-1.2E-04
Inhalation Controls	7.0E-07	2.5E-06	1.9E-05	62	-7.9E-05
Concurrent Controls	1.53E-06	Infinite	Infinite	Infinite	Infinite

(Here "DPX" refers to the estimated DPX coefficient. E.g., if this coefficient is zero, there is no mutational effect upon risk.)

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Conclusions

- This limited sensitivity analysis provided information on some aspects of the quantitative uncertainty in the CIIT formaldehyde model.
- If only NTP inhalation controls are used in rat modeling, instead of all NTP controls, human risks from hockey stick model can be 60-fold larger than in CIIT model.
- If only concurrent controls are used in rat modeling, model is not capable of bounding the human risk.

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Appendix D: Appendix H of USEPA's *Combustion Turbine Source Category Risk Characterization*, 2004

Appendix H
Derivation of Formaldehyde Risk Value

Supplement to GTA Gas Turbine Delist Petition

Rationale for Selecting Formaldehyde Risk Value Based Upon CIIT Dose-Response Assessment – 1999

Exposure Scenario: ***The maximum, worst-case exposure to formaldehyde resulting from gas turbine emissions was estimated in the GTA petition to be 0.0239 ug/m^3)*** (See GTA Petition Table 6-2, GE 7FA, Non-GEP stack height, simple terrain). An exposure of 0.0239 ug/m3 is equivalent to 0.019 ppb, as indicated in the following equation:

$ug/m^3 = ppb \times MW/24.45,$

where MW = molecular weight of compound. For formaldehyde, the molecular weight is 30, leading to:

0.0239 ug/m3 x 24.45/30 = 0.0195 ppb.

The 1999 CIIT dose-response assessment provides a range of exposure scenarios and corresponding predicted human risk values for formaldehyde exposures (see table below excerpted from CIIT). CIIT provides risk values for exposures down to 1 ppb.

The maximum exposure level predicted from gas turbines is well less than 1 ppb, but in keeping with the conservative, worst-case analysis philosophy of the GTA petition, ***GTA assumed an exposure level of 1 ppb (50 times higher than the highest modeled exposure) when selecting a formaldehyde risk value from the CIIT paper,*** in part because the CIIT paper did not provide risk values for exposures below 1 ppb.

Selection of Risk Value: Assuming an exposure level of 1 ppb from gas turbine emissions, a review of the CIIT exposure scenario table indicates a predicted human additional risk for environmental exposure of a ***smoker*** (the highest and worst-case scenario) of 4.9×10^{-9}. This value is at the lower end of the exposure scenarios provided by CIIT, and does not extrapolate linearly from higher exposure risk values, since the CIIT model assumes disproportionately lower risk with lower concentrations.

In order to be even more conservative, GTA started with the ***highest*** CIIT risk value provided for environmental exposure of a smoker (6.7×10^{-7} at 0.10 ppm (100 ppb)), and assumed a linear extrapolation down to a 1 ppb level. This produced a risk value of 6.7×10^{-9}/ppb, which is higher and more conservative than the value in the CIIT table for 1 ppb (4.9×10^{-9}). GTA believed using this higher risk value in the risk assessment would be more defensible than use of the lower value provided by CIIT.

The CIIT risk value of 6.7×10^{-9} at 1 ppb is equivalent to 5.5×10^{-9} at 1 ug/m3, according to the following equation:

$ug/m^3 = ppb \times MW/24.45$,

where MW = molecular weight of compound. For formaldehyde, the molecular weight is 30, leading to:

$ug/m^3 = 1 \text{ ppb} \times 30/24.45 = 1.23 \text{ ug/m}^3$

$6.7 \times 10^{-9} / 1.23 \text{ ug/m}^3 = 5.45 \times 10^{-9} / \text{ug/m}^3 = \mathbf{5.5 \times 10^{-9} (ug/m^3)^{-1}}$

Notwithstanding this lower calculated risk value of 5.5×10^{-9} $(ug/m^3)^{-1}$, GTA used in its risk assessment the higher value of 6.7×10^{-9} $(ug/m^3)^{-1}$, again to be more conservative, resulting in higher modeled risk than would actually be expected to occur.

This selection process by GTA results in an exposure risk value with several layers of conservatism:

1. GTA assumed an exposure concentration of 1 ppb when calculating a risk value, when conservative, worst-case modeling indicates that the highest possible exposures are actually 0.0195 ppb and less. In fact, the majority of modeling scenarios have exposures less than 0.01 ppb, or two orders of magnitude lower than the 1 ppb exposure assumed by GTA to derive a risk value.
2. GTA started with the ***highest*** CIIT risk value provided for environmental exposure of a smoker (6.7×10^{-7}at 0.10 ppm (100 ppb)), and assumed a linear extrapolation down to a 1 ppb level. GTA did not adjust this value down further to account for the conversion from ppb to ug/m^3.
3. GTA assumed the maximum exposed individual was a ***smoker,*** resulting in use of the highest and worst-case risk values in the CIIT tables.
4. GTA assumed the dose-response relationship was linear, and extrapolated down from the highest risk value provided by CIIT for environmental exposures, notwithstanding the fact that the CIIT tables would have supported use of a disproportionately lower risk value, reflecting CIIT's non-linear model with substantially lower risks at lower exposures.

Finally, it should be noted that all of the CIIT risk values for environmental exposure assume 80 years of continuous exposure, and therefore are even more conservative than the 70-year exposure scenario assumed by US EPA.

FORMALDEHYDE:

Hazard Characterization and Dose-Response Assessment for Carcinogenicity by the Route of Inhalation

REVISED EDITION

Chemical Industry Institute of Toxicology
September 28, 1999

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6 Davis Drive, Research Triangle Park, NC 27709
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Predicted human additional risk of respiratory tract cancer due to environmental and occupational exposures to formaldehyde.

Formaldehyde Exposure Concentration (ppm)	Exposure scenarios					
	Environmental[a]			Occupational[b]		
	Non-smoking	Mixed	Smoking	Non-smoking	Mixed	Smoking
0.001	$2.3X10^{-10}$	$3.9X10^{-9}$	$4.9X10^{-9}$	---[c]	---	---
0.02	$4.8X10^{-9}$	$1.0X10^{-7}$	$1.2X10^{-7}$	---	---	---
0.04	$1.0X10^{-8}$	$2.1X10^{-7}$	$2.5X10^{-7}$	---	---	---
0.06	$1.5X10^{-8}$	$3.3X10^{-7}$	$3.8X10^{-7}$	---	---	---
0.08	$2.1X10^{-8}$	$4.5X10^{-7}$	$5.3X10^{-7}$	---	---	---
0.10	$2.7X10^{-8}$	$5.8X10^{-7}$	$6.7X10^{-7}$	$4.1X10^{-9}$	$7.6X10^{-8}$	$1.0X10^{-7}$
0.30	---[c]	---	---	$1.3X10^{-8}$	$2.6X10^{-7}$	$3.8X10^{-7}$
0.50	---	---	---	$2.5X10^{-8}$	$5.0X10^{-7}$	$7.2X10^{-7}$
0.70	---	---	---	$3.4X10^{-7}$	$8.0X10^{-6}$	$6.6X10^{-6}$
1.00	---	---	---	$8.8X10^{-6}$	$2.1X10^{-4}$	$1.5X10^{-4}$

[a]80 year lifetime continuous exposure at indicated ppm.
[b]80 year lifetime continuous exposure at 0.004 ppm with 40 years occupational exposure (8hr/day, 5 days/week) at indicated ppm beginning at age 18 years. ICRP66 (1994) "light working" breathing pattern
[c]simulations not done.

The 2-stage clonal growth model is a parameter- and data-rich model in the context of cancer risk assessment. Even with the richness of the formaldehyde data, calculating all of the parameters of the clonal growth model directly from data is not possible. Some parameter values were estimated by calculating the maximum likelihood of the data. Further, there were points in the model development process where choices between alternative possible approaches were required. If insufficient

Table 8-1. Evolution of risk assessments for formaldehyde: human risk estimates for exposure to 0.1 ppm inhaled formaldehyde

Risk Assessment	Human risk at 0.1 ppm inhaled formaldehyde, 6 h/d, 5 d/wk: Risk Estimates Upper bound (MLE)	MOEs vs. LED_{01} (MLE_{01})
Clonal growth modeling[a]		
Workplace scenario[b]		
Smokers	1.0×10^{-7}	—
Nonsmokers	4.1×10^{-9}	—
Environmental scenario[c]		
Smokers	6.7×10^{-7}	—
Nonsmokers	2.7×10^{-8}	—
CIIT, BMD (1% risk)[d]		
Flux-DPX modeling		
Based on tumors	4.2×10^{-4} (3.9×10^{-4})	23.6 (25.8)
Based on labeling index	7.9×10^{-4} (5.3×10^{-4})	12.6 (18.8)
Airflow extrapolation only		
Based on tumors	2.5×10^{-4} (2.4×10^{-4})	39.9 (42.3)
Based on labeling index	3.9×10^{-4} (2.9×10^{-4})	25.5 (34.2)
EPA, 1991 (U.S. EPA, 1991)		
(rat-based, from q_1)[d]	2.8×10^{-4}	—
(rat-based, using full model)	3.1×10^{-4} (3.1×10^{-5})	—
(monkey-based, full model)	3.3×10^{-5} (4.2×10^{-7})	—
EPA, 1987 (U.S. EPA, 1987)	1.6×10^{-3} (5×10^{-7})	—

[a] Clonal growth risk estimates derived from a biologically-based model that incorporated various toxicological, mechanistic, and dosimetric data, that estimated parameters and optimized the likelihood from the data, and that provided an integrated approach to dose-response characterization.

[b] Workplace exposure scenario involved 40 years of exposure to 0.1 ppm for 8 hr per day 5 days per wk beginning at age 18. All nonwork hours from birth to age 80 involved exposure to 0.004 ppm.

[c] Environmental scenario involved 80 years of continuous exposure to 0.1 ppm.

[d] Weibull model calculation with y-intercept.

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Appendix E: Derivation of the 24-hour Reference Value for Formaldehyde

The 24-hour ReV for formaldehyde was finalized June 16, 2014

E.1 Background

For chemicals detected in the ambient air monitoring network, short-term AMCVs have generally been derived by the TCEQ to evaluate 1-h reported concentrations and long-term AMCVs have been derived to evaluate annual averages. Since a significant amount of ambient air data is collected over a 24-h duration, the derivation of chemical-specific 24-h AMCV values is needed to better evaluate ambient 24-h data. This consideration applies to formaldehyde since it is detected in the TCEQ ambient air monitoring network using 24-h dinitrophenylhydrazine cartridge samples. Without a 24-h AMCV for formaldehyde, only a very limited evaluation of the reported 24-h levels is possible because 1-h and chronic (i.e., lifetime) AMCVs are generally inappropriate for this purpose. Thus, the development of a 24-h AMCV is necessary for the best possible health effects evaluation of individual 24-h sample results, and would significantly complement the short-term and chronic evaluations of formaldehyde ambient air data.

A 24-h ReV is derived for human health hazards associated with threshold dose-response relationships (typically effects other than cancer) and is defined as an estimate of an inhalation exposure concentration that is likely to be without an appreciable risk of adverse effects to the human population (including susceptible subgroups) for a 24-h exposure. The ReV is used as the AMCV (TCEQ 2012). The critical step in deciding whether or not to derive a 24-h AMCV is the availability of appropriate toxicity studies that provide meaningful information for evaluation of a 24-h exposure duration. An evaluation of the mode of action, dose metric, and the toxicokinetics and toxicodynamics of the chemical as well as exposure duration adjustments that are unique for the derivation of a 24-h AMCV is conducted. The same analytical steps used to derive acute 1-h AMCVs and chronic AMCVs (TCEQ 2012) are used to derive a 24-h AMCV (TCEQ 2014; 2015). OECD (2010) also provides guidance applicable to the development of acute reference concentrations.

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

- availability of appropriate toxicity studies that provide meaningful information to evaluate a 24-h exposure duration;
- identification and review of appropriate toxicity studies;
- identification of a point of departure for the critical effect(s) based on review of dose-response data for relevant toxicity endpoints;
- consideration of an exposure duration adjustment;

- animal-to-human inhalation dosimetric adjustment (if applicable);
- selection and application of applicable uncertainty factors; and
- derivation of the 24-h AMCV.

Please refer to Section 3.1 for detailed information on human and animal studies, mode of action information, etc.

E.2 Acute 24-h AMCV

Both human and animal noncarcinogenic studies indicate that the critical target organs for airborne formaldehyde are the nose and eyes, with the lungs being a secondary target at much higher concentrations (ATSDR 1999). In other words, in both human studies (e.g., acute, occupational, residential) and animal studies (i.e., acute, intermediate, chronic), the most sensitive or critical endpoint for exposure to formaldehyde is irritation of the eyes and upper respiratory tract (i.e., nasopharyx, oral cavity, and throat), nose and throat irritation more specifically, with the eye generally being most sensitive (ATSDR 1999, Noisel et al. 2007).

E.2.1 Key and Supporting Studies

Acute studies with exposure durations less than 24 h are appropriate for use as the basis for a 24-h AMCV when, for example, available data indicate that the adverse effect induced by the chemical is primarily concentration-dependent (e.g., sensory irritation induced at the point of entry) and 24-h exposure would not be expected to result in a different adverse effect (TCEQ 2014; 2015). This is the case for formalehyde-induced sensory irritation. For example, acute to chronic exposure (in both humans and laboratory animals) results in the same critical effect of formaldehyde-induced sensory irritation, and there is no indication that extending exposure beyond typical acute study exposure durations (e.g., 1-4 hours) would increase formaldehyde irritative response or sensitivity (ATSDR 1999, WHO 2010).

Since relevant human studies are available and preferable over animal studies, human studies were reviewed and used to develop the 24-h AMCV. Studies of humans under controlled conditions clearly indicate that acute (short-term) exposures to air concentrations ranging from 0.4 to 3 ppm induce reversible mild to moderate eye, nose, and throat irritation, produce changes in nasal lavage fluid contents indicative of irritation of the nasal epithelium, and do not consistently or markedly affect pulmonary function variables in most individuals (ATSDR 1999). Controlled human exposure studies provide the best dose-response data on the irritancy of formaldehyde for quantitative risk assessment (NAS/NRC 1980). Two such studies, Pazdrak et al. (1993) and Krakowiak et al. (1998), are used as key studies for derivation of the 24-h AMCV. Other studies were also reviewed for potential use as supporting studies (e.g., Kulle et al. 1987 and 1993, Lang et al. 2008, Mueller et al. 2013). The key studies are supported by the studies of Kulle et al. (1987, 1993) and Lang et al. (2008). These are the same key and supporting studies used to develop the acute 1-h AMCV and their study summaries were taken from TCEQ (2008).

E.2.1.1 Key Studies

E.2.1.1.1 Pazdrak et al. (1993)

The Pazdrak et al. (1993) study was also used by ATSDR (1999) as a key study in derivation of the acute inhalation minimal risk level (MRL) for up to 14 days of exposure to formaldehyde. Pazdrak et al. (1993) exposed 20 volunteers, nine of whom had skin hypersensitivity to formaldehyde, to 0.5 mg/m^3 (0.4 ppm) formaldehyde for 2 h. This exposure concentration is below the lower level of odor detection (0.5 ppm) as determined from properly conducted human volunteer chamber studies (ATSDR 2008 as cited by Golden 2011). Clean air served as placebo. Symptoms of rhinitis (i.e., number of sneezes, degree of mucosal edema, rhinorrhea, itching) were measured and scored. Nasal lavage was performed before exposure, immediately after, and 4 and 18 h after exposure had ended. Morphological (e.g., cell number, differential count) and biochemical (e.g., albumin and total protein levels) changes in nasal lavage fluid were evaluated. The total number of eosinophils and basophils (metachromatic cells) were determined, and the differential count determined number of epithelial cells, eosinophils, neutrophils, basophils, and mononuclear cells (includes lymphocytes and monocytes) per 200 cells. The study showed transient burning sensation of the eyes and nasal passages, transient symptoms of rhinitis (i.e., increased itching, sneezing, and congestion), and nasal washing changes (i.e., increased eosinophil count/proportion, albumin, and total protein levels) at 0.5 mg/m^3 (0.4 ppm). Tryptase concentration in nasal lavage was also measured but did not show any increase. Tryptase is involved in the allergic response, the most abundant secretory granule-derived serine protease contained in mast cells, and a measure of mast cell degranulation. The study authors concluded that the lack of evidence for mast cell degranulation (release of inflammation mediators such as histamine), the unchanged number of basophils, and the similarity of responses in healthy and sensitized subjects indicate the occurrence of nonspecific, nonallergic inflammatory processes in the nasal mucosa. *The lowest-observed-adverse-effect level (LOAEL) from Pazdrak et al. (1993) is 0.5 mg/m^3 (0.4 ppm) based on transient burning sensation of the eyes and nasal passages and transient symptoms of rhinitis.*

E.2.1.1.2 Krakowiak et al. (1998)

Krakowiak et al. (1998) is a relevant study for the 24-h AMCV and is discussed in the supporting documentation for the 1-14 day acute inhalation MRL (ATSDR 1999). Krakowiak et al. exposed 20 volunteers to 0.5 mg/m^3 (0.4 ppm) formaldehyde for 2 h. Ten of the volunteers had occupational exposure to formaldehyde, had historically experienced rhinitis and asthmatic symptoms in the workplace, were suspected of having respiratory formaldehyde sensitization, and had been diagnosed with bronchial asthma probably being due to formaldehyde exposure (i.e., formaldehyde-induced asthma). Clean air served as placebo. Nasal symptoms (i.e., number of sneezes, degree of mucosal edema, rhinorrhea, itching) were measured and scored. The occurrence and intensity of clinical symptoms from the lower respiratory tract (i.e., coughing, dyspnea (shortness of breath)) were also recorded. Nasal lavage was performed before exposure, immediately after, and 4 and 24 h after exposure had ended. Morphological changes in nasal lavage fluid were evaluated. The total number of eosinophils and basophils (metachromatic cells) were determined, and the differential count determined number of epithelial cells, eosinophils, basophils, and mononuclear cells (includes lymphocytes and monocytes) per 200 cells. Biochemical (e.g., albumin, total protein, tryptase, and eosinophil cationic protein levels)

changes in nasal lavage fluid were also evaluated. Bronchial response was measured by spirometry. Forced expiratory volume in 1 second (FEV_1) was measured prior to exposure, immediately after, and 5 and 24 h after exposure. Peak expiratory flow (PEF) was measured at the beginning of exposure and every hour for 12 h, and again at 24 h after exposure. A histamine inhalation test utilizing various concentrations (0.03, 0.06, 0.125, 0.250, 0.5, 1, 2, 4, 8, and 16 mg/ml) and FEV_1 measurements was performed at the beginning of exposure, 5 minutes into the exposure, and 24 h after exposure. $PC_{20}H$ was defined as the histamine dose producing a twenty percent decrease in FEV_1. Total serum immunoglobulin gamma E (IgE) and formaldehyde-specific serum IgE antibodies were measured.

The 0.4 ppm exposure in Krakowiak et al. (1998) produced transient symptoms of rhinitis (i.e., increased sneezing, itching, and congestion) in all subjects, which were most severe immediately after inhalation (less severe 4 h later). There was no significant difference in nasal response between healthy subjects and asthmatic subjects occupationally exposed to formaldehyde. A typical allergen challenge triggers both the influx of mast cells and eosinophils (leukocytes which play major roles in allergic and inflammatory responses), and the pronounced increase in the concentrations of their respective enzymes, tryptase and eosinophil cationic protein. Combined, these may be used as markers of nasal allergic reaction. The number of eosinophils and leukocytes increased following exposure, while the levels of tryptase and eosinophil cationic protein did not. Regarding pulmonary function, no asthmatic subjects developed clinical symptoms of bronchial irritation, and there were no significant changes in FEV_1, PEF, or $PC_{20}H$ values in healthy or asthmatic subjects due to formaldehyde exposure, although the baseline FEV_1 and PEF values for healthy and asthmatic subjects differed. Formaldehyde did not increase the bronchial response to histamine ($PC_{20}H$) in asthmatic subjects. No formaldehyde-specific IgE antibodies were detected in asthmatic subjects with occupational exposure. The authors concluded that the lack of evidence for mast cell and eosinophil degranulation and the similarity of responses in healthy and asthmatic subjects indicate the occurrence of nonspecific, nonallergic inflammatory processes in the nasal mucosa. *The LOAEL from Krakowiak et al. (1998) is 0.5 mg/m^3 (0.4 ppm) based on transient symptoms of rhinitis (i.e., increased sneezing, itching, and congestion).*

E.2.1.2 Supporting Studies

E.2.1.2.1 Kulle et al. (1987, 1993)

Pazdrak et al. (1993) and Krakowiak et al. (1998) are supported by Kulle et al. (1987, 1993), which had a no-observed-adverse-effect-level (NOAEL) for eye irritation (0.5 ppm) higher than the LOAELs from the two key studies (0.4 ppm). Kulle et al. (1987, 1993) examined pulmonary function and irritant symptoms in 19 volunteers exposed to up to 3 ppm at rest (plus 2 ppm when exercising) for 3 h. Exposure groups included formaldehyde concentrations of 0, 0.5, 1.0, 2.0, and 3.0 ppm. There were no significant decreases in pulmonary function or increases in bronchial reactivity in response to methacholine. Exercise significantly increased nose/throat irritation. Nasal flow resistance was increased at 3.0 ppm. Significant dose-response relationships in odor and eye irritation were observed. Mild eye irritation (21% of subjects) and moderate eye irritation (5% of subjects) were observed at 1 ppm but not 0.5 ppm. Kulle (1993) reexamined the response data with additional statistical methodology and estimated threshold levels as 0.5 to 1.0 ppm for eye irritation and 1.0 ppm for nose/throat irritation. *The LOAEL and*

NOAEL based on eye irritation in the supporting study of Kulle et al. (1987, 1993) are 1 ppm and 0.5 ppm, respectively.

Data from Kulle et al. (1993) are amenable to benchmark dose (BMD) modeling. Therefore, the Toxicology Division (TD) of the TCEQ performed BMD modeling on the eye irritation data (i.e., mild, moderate, mild/moderate combined) presented in Table 3 of Kulle et al. (1993) using USEPA BMD Modeling Software (see TCEQ 2008). Goodness of fit was evaluated by visual inspection with scaled residuals < 2 and goodness-of-fit p values > 0.1, and several models appeared to fit the data adequately. Benchmark concentration low (BMCL) values corresponding to the 5% response level ($BMCL_{05}$) for extra risk at the 95% confidence level were approximately 0.305-0.363 ppm for mild eye irritation and 0.611-0.652 ppm for moderate eye irritation, while $BMCL_{05}$ values for mild/moderate combined were slightly lower at 0.286-0.329 ppm (see Appendix 1 of TCEQ 2008).

Eye irritation based on mild/moderate combined was selected as the endpoint of concern from Kulle et al. (1987, 1993). While several models had adequate goodness of fit, the probit and logistic models had lower (and similar) AIC values, indicating a better fit. The $BMCL_{05}$ values from these two models (0.286 and 0.316 ppm) were averaged to give a human point-of-departure value (POD_{HEC}) value of 0.30 ppm. This value is similar to the study NOAEL (0.5 ppm) at which 0% of the study participants responded. The California Environmental Protection Agency (CalEPA) calculated a similar $BMCL_{05}$ (0.44 ppm) based on the probit model and the Kulle et al. data for derivation of the 2008 acute reference exposure level (REL) (CalEPA 2008).

E.2.1.2.2 Lang et al. (2008)

The key studies are also supported by Lang et al. (2008), which had a reported NOAEL for eye irritation of 0.5 ppm for a 4-h exposure with no peak exposures. This reported NOAEL is higher than the LOAELs of 0.4 ppm from the two key studies. Lang et al. (2008) examined sensory irritation (objective and subjective measures), nasal flow and resistance, pulmonary function (e.g., PEF, FEV_1), reaction time, and personality factors in 21 healthy human subjects exposed for 4 h to 10 different exposure conditions. The exposure conditions included target formaldehyde concentrations of 0.15, 0.3, or 0.5 ppm, with or without four formaldehyde peaks of 0.6 or 1 ppm, and in the presence or absence of ethyl acetate (12-16 ppm) as an odorous masking agent (see Table 1 of Lang et al. 2008). The study data most applicable for supporting derivation of the 24-h AMCV is that based on exposure without peaks, although a discussion of the results of exposure with peaks is also provided. Actual analytical exposure levels are reported in Table 6 of the study. Control exposure was either to 0 ppm formaldehyde or 0 ppm formaldehyde with the addition of ethyl acetate as an odorous masking agent, which was reported not to be an irritant at the concentrations used. The perception of odors may cause increased reporting of irritation due to insufficient distinction between olfactory stimulation and trigeminal nerve-induced irritation. Objective measures of sensory irritation included ophthalmologic grading of conjunctival mucosa redness (e.g., 1=very slight to 4=severe) and blinking frequency (blinks per 90 seconds), and subjective measures included scores for eye/nose/respiratory irritation and olfactory symptoms (e.g., 1=slight to 5=very strong) as reported on complaint questionnaires (see Table 3 of Lang et al. 2008).

Exposures without peaks: There were no significant differences in nasal resistance/flow or

pulmonary function. Decision reaction time in response to a visual and/or acoustic stimulus, but not motor reaction time (i.e., movement time), was significantly increased in the 0.3 ppm exposure group. However, this was not observed in any of the 0.5 ppm formaldehyde exposure groups and was not considered exposure-related. Reported eye irritation was significantly increased at 0.3 and 0.5 ppm formaldehyde as compared to the 0 ppm control exposure. However, reported eye irritation was not increased at 0.3 or 0.5 ppm formaldehyde as compared to the 0 ppm plus masking agent control exposure. Consequently, the study authors apparently did not consider 0.3 or 0.5 ppm formaldehyde as the LOAEL for eye irritation (i.e., the increased reporting could have been due to the perception of formaldehyde's odor). *The authors of this supporting study report the NOAEL based on objective and subjective measures of eye irritation to be 0.5 ppm for exposure without peaks.*

Exposures with peaks: Nasal resistance/flow and pulmonary function did not show significant differences. Significantly increased nasal irritation was reported at 0.3 ppm with 0.6 ppm peaks (and 0.5 ppm with 1 ppm peaks) as compared to both control groups (i.e., 0 ppm formaldehyde and 0 ppm plus masking agent). Statistically increased conjunctival redness and blinking frequency were observed at 0.5 ppm with four 1 ppm peaks, but not in any of the 0.3 ppm formaldehyde groups. Eye irritation was significantly increased at 0.3 ppm with 0.6 ppm peaks (and 0.5 ppm with 1 ppm peaks) as compared to the 0 ppm plus masking agent control exposure. However, eye irritation at 0.3 ppm with 0.6 ppm peaks was not reported to also be significantly increased compared to the 0 ppm group, although it seems it should be based upon examination of Figure 7 of the study.

The finding of significantly increased reported eye irritation in the 0.3-0.6 ppm range in this study (i.e., 0.3 ppm with 0.6 ppm peaks compared to the 0 ppm plus masking agent control, 0.3 and 0.5 ppm compared to the 0 ppm control) lends some support to the eye irritation LOAEL of 0.4 ppm from the Pazdrak et al. (1993) key study.

E.3 Mode of Action (MOA) and Dose Metric

The MOA by which formaldehyde may produce noncarcinogenic effects (e.g., eye/respiratory irritation) is discussed in TCEQ (2008). For the key and supporting studies, data on formaldehyde air concentrations are available. Formaldehyde air concentration is an appropriate dose metric for the acute noncarcinogenic evaluation for the 24-h AMCV as air concentration is the dominant determinant of irritation.

E.4 Critical Effects and Point of Departure

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

For the acute assessment of formaldehyde, key and supporting studies indicate sensory irritation

to be the critical effect. More specifically, the key studies of Pazdrak et al. (1993) and Krakowiak et al. (1998) provide the lowest POD_{HEC} value associated with effects (LOAEL of 0.5 mg/m^3 or 0.4 ppm) and identify eye and nose irritation and symptoms of rhinitis (e.g., increased itching, sneezing and congestion) as the specific sensory irritation critical effects for this assessment. Thus, the POD_{HEC} of 0.4 ppm (LOAEL) will be used to derive the 24-h AMCV.

Pazdrak et al. (1993) and Krakowiak et al. (1998) key studies:

POD_{HEC} = 0.5 mg/m^3 (0.4 ppm) (LOAEL)

E.5 Potential Duration Adjustments

An exposure duration adjustment is judged not to be necessary because air concentration is the dominant determinant of formaldehyde-induced irritation (TCEQ 2014, 2015; Golden 2011). This is consistent with other agencies (e.g., derivation of the 1-14 day acute inhalation MRL by ATSDR 1999).

E.6 Uncertainty Factors and Derivation of the 24-h ReV

The default procedure for deriving health-protective concentrations for noncarcinogenic effects is to determine a POD and apply appropriate uncertainty factors (UFs) (i.e., assume a threshold/nonlinear MOA) (TCEQ 2012). The LOAEL from the Pazdrak et al. (1993) and Krakowiak et al. (1998) key studies (0.5 mg/m^3) was used as the POD_{HEC} and divided by the following UF (total UF=10, consistent with TCEQ 2008):

- A LOAEL-to-NOAEL UF_L of 3;
- An intrahuman variability UF_H of 3; and
- A database uncertainty UF_D of 1.

A UF_L of 3 was used since the LOAEL is considered minimal due to the mild symptoms observed (mild and reversible irritant effects; see Table B-2 of TCEQ 2012), and the clinical significance of changes in the nasal lavage fluid is uncertain. This is consistent with ATSDR (1999), which utilized a UF_L of 3 with Pazdrak et al. (1993) for use of a minimal LOAEL in calculating the acute (1-14 day) inhalation MRL.

A UF_H of 3 was used for intrahuman variability since the irritant effects were observed in studies which included potentially sensitive subpopulations (i.e., formaldehyde sensitized or potentially sensitized individuals). However, a value of 1 was not used since data suggest other potentially sensitive subpopulations which were not included. For example, ocular irritation was significantly ($p < 0.001$) higher among wearers of contact lenses compared with students without contacts in Tanaka et al. 2003 (as cited by CalEPA 2008). Thus, although the key studies included potentially sensitive subpopulations, some uncertainty about intraspecies differences in sensitivity remains and use of a UF_H greater than 1 (e.g., 3) is justified.

A UF_D of 1 was used because the overall toxicological database for formaldehyde is extensive.

The acute database contains numerous inhalation studies in both humans and animals examining a range of potential formaldehyde-induced effects both more serious (e.g., nasal epithelial necrosis, hyperplasia, squamous metaplasia, increased cell proliferation, ciliary destruction) and less serious (e.g., eye, nose, throat irritation, small changes in pulmonary function) in nature. Several human studies have included potentially sensitive individuals (e.g., asthmatics, those otherwise identified as sensitive). Among animal studies, several species/strains have been utilized (e.g., rats, mice, guinea pigs), including monkeys, and information on the potential for developmental/reproductive effects is also available (ATSDR 1999).

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

$$= 0.5 \text{ mg/m}^3 / (3 \times 3 \times 1)$$

$$= 0.5 \text{ mg/m}^3 / (10)$$

$$= 0.05 \text{ mg/m}^3 \text{ or } 50 \text{ µg/m}^3$$

Table 9 shows a summary of the derivation of the 24-h AMCV

Table 9 Derivation of the Acute 24-H AMCV

Parameter	**Summary**
Study	Pazdrak et al. (1993) and Krakowiak et al. (1998)
Study population	Pazdrak et al. (1993): 20 human volunteers (9 with skin hypersensitivity to formaldehyde); Krakowiak et al. (1998): 20 human volunteers (10 with bronchial asthma and suspected respiratory formaldehyde sensitization)
Study quality	medium
Exposure Methods	0.5 mg/m^3 (0.4 ppm) formaldehyde for 2 h
Critical Effects	Eye and nose irritation, symptoms of rhinitis
POD_{HEC}	LOAEL of 0.5 mg/m^3 (0.4 ppm)
Extrapolation to 24 h	Not Applicable, effects concentration dependent
24-h POD_{HEC}	0.5 mg/m^3
Total UFs	10
Intraspecies UF	3
LOAEL UF	3
Incomplete Database UF	1
Database Quality	*high*
Acute 24-h ReV (HQ =1) **Acute 24-h AMCV**	50 µg/m^3 (41 ppb)

E.7 Values for Air Monitoring Evaluation

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

- 1-h acute health-based AMCV = 50 µg/m^3 (41 ppb) (TCEQ 2008)
- 24-h acute health-based AMCV = 50 µg/m^3 (41 ppb)
- 1-h acute odor-based AMCV = 610 µg/m^3 (500 ppb) (TCEQ 2008)

The 24-h AMCV of 50 µg/m^3 (41 ppb) may be used for the evaluation of 24-h ambient air monitoring data (Table 1). It is sufficiently conservative to protect public health against the potential adverse effects of formaldehyde due to 24-h exposure and would significantly complement TCEQ health effect evaluations of ambient air data, which currently utilize 1-h and chronic (i.e., lifetime) health-protective and welfare-based (i.e., odor, vegetation) AMCVs.

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