MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 18, 2014

TO: File for Formaldehyde (CAS No. 50-00-0)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Acute Screening Level Update

The acute initial threshold screening level (ITSL) for formaldehyde is being established at 30 µg/m³ (24-hr averaging time). An IRSL and SRSL were previously established at 0.08 and 0.8 ug/m3 (annual averaging time), respectively. An acute ITSL is deemed appropriate to help ensure protection from potential acute toxic effects from formaldehyde exposure.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), and the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ATSDR), Texas Commission on Environmental Quality (TCEQ) and California Office of Environmental Health Hazard Assessment (Cal OEHHA). The EPA has not established an acute or chronic non-cancer reference concentration (RfC) for formaldehyde. The relevant health benchmarks available at this time are shown in Table 1 and Table 2.

EPA (2012) defines an Acute Reference Concentration (RfC) as follows:

> An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for an acute duration (24 hours or less) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used.

Physical Properties of Formaldehyde

1. The molecular weight of formaldehyde is 30.03 g
    a. Vapor Pressure
        i. 101.3 kPa (760 mmHg) at -19 °C (-2.2 °F)(WHO, 1989)
        ii. 52.6 kPa (395 mmHg) at -33 °C (-27 °F) (WHO, 1989)
        iii. 511.0 kPa (3833 mmHg) at 25 °C (77 °F) (ATSDR, 1999)
2. Odor Threshold = 0.5-1.0 ppm (ATSDR, 1999)
3. Conversion: 1 ppb = 1.23 ug/m3 (TCEQ, 2014)
4. Photolysis half-life (in sunlight) = 1.6–19 hours producing H_2 and CO or H+ and HCO (ATSDR, 1999)
5. Chemical Structure:

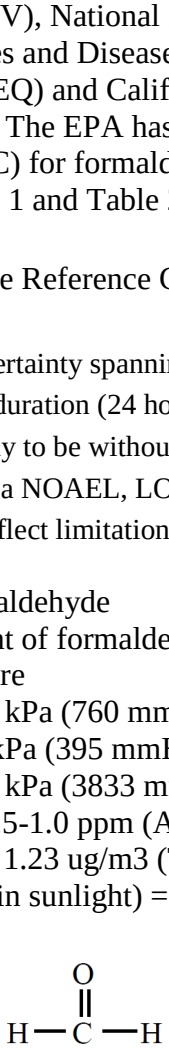

Table 1. Health Benchmarks for Acute Exposures to Formaldehyde

Benchmark	**Organization Name** *(averaging time specified)*	**Benchmark Value** (µg/m³)	**Benchmark Value** (ppm)	**Averaging Time** (hrs)
Ceiling-Recommended Exposure Level (c-REL)	National Institute of Occupational Safety and Health (NIOSH) *(specified: 15 min.)*	123	0.1	0.25
Ceiling-Threshold Limit Value (c-TLV)	American Conference of Governmental Industrial Hygienists (ACGIH) *(specified: not to be exceeded)*	370	0.3	not to be exceeded
Short Term Exposure Limit (STEL)	Occupational Safety and Health Administration (OSHA) *(specified: 15 minute)*	2460	2	0.25
Air Quality Guideline	World Health Organization (WHO) *(Specified: 30 minutes)*	100	0.08	0.5
Acute REL	California Environmental Protection Agency (Cal EPA) *(specified: 1-hr)*	55	0.044	1
8-hr REL	Cal EPA *(specified: 8-hr)*	9	0.007	8
Home Indoor	U.S. Housing and Urban Development (HUD) *(not specified: 8-hr?)*	500	0.4	8
Maximum Concentration	U.S. Federal Emergency Management Agency (FEMA) *(specified: 8-hr) For indoor air.*	20	0.016	8
Permissible Exposure Limit	OSHA *(specified: 8-hr)*	920	0.75	8
REL	NIOSH *(specified: 10-hr)*	20	0.016	8
Acute Minimal Risk Level	Agency for Toxic Substances and Disease Registry (ATSDR) *(specified: up to 14 days)*	50	0.04	24
Reference Value (proposed 2014)	Texas Commission on Environmental Quality (TCEQ) *(specified:24-hr)*	30	0.024	24
Reference Value	Texas Commission on Environmental Quality (TCEQ)	50	41	1

Table 2. Acute Exposure Guidance Level-1 (AEGL-1) for Transient, Reversible Effects

10 minute	**30 minute**	**60 minute**	**4 hours**	**8 hours**
0.9 ppm	0.9 ppm	0.9 ppm	0.9 ppm	0.9 ppm
1,000 µg/m³	1,000 µg/m³	1,000 µg/m³	1,000 µg/m³	1,000 µg/m³

As shown in Table 1 the acute health benchmarks range from 9 µg/m³ to 2460 µg/m³. Typically benchmarks with short averaging times are higher than those with longer averaging times;

however, this is not always the case. Benchmarks can differ based on the human population intended to protect (e.g., sensitive individuals, healthy workers), definition of "adverse effect", the level of protection, and other quantitative/qualitative adjustments (e.g., repeated exposures over lifetime, single short-term exposure, professional judgment). Occupational exposure limits (OELs) derived by OSHA, NIOSH and ACGIH have 15-minute or 8-hr time weighted average (TWA) exposure durations (except NIOSH specifies a 10-hr TWA, but is usually interpreted as 8-hr TWA). OELs are designed to protect healthy workers. Table 2 shows the interim EPA Acute Exposure Guidance Levels (AEGLs) for formaldehyde. An AEGL-1 is defined as

> AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

These are intended to protect against health effects from non-recurring exposures for the specified time periods, i.e., 10-minutes to 8-hours. All the interim AEGL-1 values for formaldehyde are 1000 $\mu g/m^3$. The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) provides additional information on AEGLs:

> Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

The AEGL-1 benchmark allows for the possibility that individuals could experience unique or idiosyncratic responses below the AEGL-1, and allows for the possibility that all individuals may experience sensory irritation or non-sensory effects. Therefore, the applicability of AEGLs in an air permit program, which allows facilities to emit the pollutant at levels for many years, typically 30 years or more, should also be scrutinized for protectiveness for long-term exposure durations or consider the ability of individuals to recover during non-exposed intervals. AEGLs are intended to inform emergency response activities rather than the identification of acceptable exposures that may be recurring due to an ongoing emission source. AEGLs were not included in Table 1 for the reason that benchmarks in Table 1 imply recurring exposures (e.g., OELs for occupational lifetime $\geq$ 40yrs) for the specified averaging times.

Background on Use of Acute ITSLs by the Air Quality Division

Because the MDEQ-Air Quality Division Air Permitting Program issues air pollution permits to install that do not expire, the acute ITSL must take into account not only the effects from a single short-term exposure, but also those short exposures that may recur over a lifetime. Averaging times for acute ITSLs are 24-hours or less (e.g., 24-hr, 8-hr or 1-hr). With this in mind the acute benchmarks derived from several agencies were evaluated. The benchmarks that were given higher weight for a candidate ITSL were assessed based on how well they were derived, using characteristics such as:

- Protect, including sensitive individuals, from acute adverse health effects
- Account for short-term exposures that may recur
- Provide analysis and discussion of the toxicological database of effects, and
- Use peer reviews for consensus benchmarks

OELs, as derived by ACGIH, NIOSH and OSHA, provide a suitable health benchmark with which to derive an acute ITSL (with the application of an uncertainty factor) only when higher quality benchmarks are not available.

Three benchmarks from Table 1 were found to best use the characteristics bulleted above:

1. Agency for Toxic Substances and Disease Registry (ATSDR)
2. California Environmental Protection Agency (Cal EPA)
3. Texas Commission on Environmental Quality (TCEQ)

ATSDR Acute Minimal Risk Level (MRL)

The Agency for Toxics Substances and Disease Registry (ATSDR, 1999) derived an acute Minimal Risk Level (MRL) for formaldehyde as 50 ug/m³ (0.04 ppm); acute MRLs have an averaging time of up to 14 days. The acute MRL is derived from human data "Changes in Nasal Lavage Fluid Due to Formaldehyde Inhalation" (Pazdrak et al., 1993). This study investigated the effects of formaldehyde exposure on the severity of symptoms of nasal and eye irritation and the cellular makeup of nasal discharge in occupationally exposed patients with skin hypersensitivity to formaldehyde and unexposed (control) patients. The study was comprised of 2 study groups, all of whom were non-smokers. Group 1 consisted of 7 male and 3 female volunteers, all of whom suffered from skin hypersensitivity to formaldehyde; group 2 consisted of 11 healthy males with no history of allergic diseases, normal serum IgE levels, and negative skin tests to common allergens. Nasal washings were performed in both groups immediately before and after a 2-hour exposure to 0 (placebo) and 0.5 mg/m³ (0.4 ppm) formaldehyde, and at 4 and 18 hours after completion of the 2-hour exposure periods. RESULTS: Exposure to 0.4 ppm formaldehyde showed statistically significantly increased average symptom scores compared with average placebo scores (about 4 versus <0.5). Symptom scores were no longer elevated 18 hours after exposure. Eosinophil counts were elevated at all time points after 0.4 ppm formaldehyde exposure, while the proportion of epithelial cells declined after formaldehyde exposure. Albumin levels also increased after formaldehyde exposure, but remained elevated only briefly (10 minutes). There were no significant differences between allergic and healthy patients in nasal washing characteristics after formaldehyde exposure. No changes in basophil numbers were noted in either patient group and there was no evidence of mast cell degranulation. The authors concluded that the symptoms observed were the result of a non-specific, non-allergic process in response to low-level formaldehyde vapor exposure. The authors also noted that further study is required to understand the significance of the increased release of eosinophils noting that eosinophils may have both protective (e.g., they can neutralize histamine) and damaging (e.g., they may liberate mediators that damage epithelial surfaces) properties.

Irritation (to eyes, nose) seems to be a less serious "adverse" effect and therefore should require less uncertainty adjustment, however, it is not known whether this should diminish the inter-individual uncertainty factor which is typically 3 for less serious effects.

The only concentration tested, 0.4 ppm, is a minimal lowest-observed-adverse-effect-level (LOAEL) for nasal and eye irritation. Extrapolation from animals to humans was not warranted because the study was performed in humans. The total Uncertainty Factor (UF) for derivation of the MRL was 10 (3 x 3; or $(10)^{0.5}$ x $(10)^{0.5}$).

$MRL = LOAEL/(UF_1 \times UF_2)$

Where:

UF_1 = 3 for human variability was used because the symptoms of irritation were observed in a potentially sensitive group of subjects (they displayed dermal sensitivity to formaldehyde).
UF_2 = 3 for extrapolation of a minimal LOAEL to No-Observable-Adverse-Effect-Level (NOAEL), because the observed symptoms of irritation were mild and reversible, and the clinical significance of the changes in nasal lavage fluid content is uncertain at present.

MRL = 0.4 ppm/10
MRL = 0.04 ppm

Conversion of ppm to µg/m³:

µg/m³ = (ppm x Molecular Weight)/24.45 x 1000 µg/mg
= (0.04 ppm x 30.03)/24.45 x 1000 µg/mg
= 49.1 µg/m³

Rounding to 1 significant figure yields MRL = 5×10^1 or 5E+1 µg/m³.

CAL-OEHHA REL

The following excerpts of text are taken directly from the CAL-OEHHA 2008 document for Derivation of the Formaldehyde REL (Recommended Exposure Level)(Cal OEHHA, 2008).

The non-cancer adverse health effects of formaldehyde are largely a manifestation of its ability to irritate mucous membranes. As a result of its solubility in water and high reactivity, formaldehyde is efficiently absorbed into the mucous layers protecting the eyes and respiratory tract where it rapidly reacts, leading primarily to localized irritation. Acute high exposure may lead to eye, nose and throat irritation, and in the respiratory tract, nasal obstruction, pulmonary edema and dyspnea. Prolonged or repeated exposures have been associated with allergic sensitization, respiratory symptoms (coughing, wheezing, shortness of breath), histopathological changes in respiratory epithelium, and decrements in lung function. Children, especially those with diagnosed asthma, may be more likely to show impaired pulmonary function and symptoms than are adults following chronic exposure to formaldehyde. The studies reviewed for this document include those published through the Spring of 2008.

Metabolism

Inhaled formaldehyde reacts rapidly at the site of contact and is efficiently absorbed in the respiratory tract. A portion of the formaldehyde entering the fluid layer covering the respiratory epithelium, the respiratory tract lining fluid (RTLF), is reversibly hydrated to methylene glycol. Both the hydrated and unreacted formaldehyde may be absorbed into the epithelial layer where there is further opportunity for formaldehyde to bind to glutathione. This glutathione conjugate in turn is oxidized to *S*-formylglutathione by formaldehyde dehydrogenase. Hydrolysis of *S*-formylglutathione yields formate and glutathione. Formic acid may be eliminated in urine and feces, or dehydrogenated to CO2 and exhaled. The presence of glutathione and formaldehyde dehydrogenase in epithelial cells of the respiratory tract varies with location and influences the amount of formaldehyde reaching the blood. While glutathione-bound formaldehyde is rapidly metabolized, free formaldehyde in cells can form DNA-protein cross-links (Franks, 2005).

Acute Toxicity of Formaldehyde

The acute effects of formaldehyde exposure appear to be largely a result of its irritant properties. However, some individuals experience symptoms following acute exposures that are a result of previous sensitization following acute high formaldehyde exposure, or long term low level exposures. Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritative and pulmonary effects.

Kulle et al (1987) was chosen as the critical study for the determination of the 1-hr REL as it used a sensitive endpoint, eye irritation. It featured human subjects showing significant ($p < 0.05$) responses with short-term exposures to a range of formaldehyde concentrations, and the data permitted the use of a benchmark concentration (BMC) approach. As described in the technical support document, OEHHA recommends the use of the BMC approach whenever the available data support it as the BMC method provides a more statistically sound estimate of the point of departure in the REL determination.

The 1-hr REL was based on a $BMCL_{05}$ for eye irritation, estimated using log-probit analysis (Crump, 1984). The $BMCL_{05}$ is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting $BMCL_{05}$ from this analysis was 0.44 ppm (0.53 mg/m^3) formaldehyde. The endpoint of eye irritancy appears to be more a function of formaldehyde concentration rather than duration of exposure (Yang et al., 2001), so no time correction factor was applied.

Table 4. CAL-OEHHA 1-hr REL: Key Study and Decision Points

Study	Kulle et al., 1987
Study population	19 nonasthmatic, nonsmoking humans
Exposure method	Whole body to 0.5-3.0 ppm
Exposure continuity	Single exposure per concentration
Exposure duration	3 hr
Critical effects	mild and moderate eye irritation
LOAEL	1 ppm
NOAEL	0.5 ppm
Benchmark concentration	0.44 ppm
Time-adjusted exposure	not applied
Human Equivalent Concentration	not applied
LOAEL uncertainty factor (UF_L)	not applied
Subchronic uncertainty factor (UF_S)	not applied
Annimal Toxicokinetic (UF_{A-K})	1 (default, human study)
Annimal Toxicodynamic (Uf_{A-d})	1 (default, human study)
Human Toxicokinetic (UF_{H-K})	1 (site of contact; no systemic effects)
Human Toxicodynamic (UF_{H-d})	10 (asthma exacerbation in children)
Cumulative uncertainty factor	10
Reference Exposure Level	55 μg/m^3 (44 ppb)

An uncertainty factor (UF_{H-k}) of 1 was used since sensory irritation is not expected to involve large toxicokinetic differences among individuals. Although the toxicological endpoint is eye irritation, the REL should protect against all possible adverse effects. The respiratory irritant effect, with documented potential to exacerbate asthma, is clearly an

effect with the potential to differentially impact infants and children. In addition, the ability of formaldehyde to exacerbate the immune response to aeroallergens is of especial concern during development of the lungs. The toxicodynamic component of the intraspecies uncertainty factor $UF_{H\text{-}d}$ is therefore assigned an increased value of 10 to account for potential asthma exacerbation.

The 8-hour REL is based on the occupational study by Wilhelmsson and Holmstrom (1992). This study evaluated the effects of formaldehyde on the upper airways of adult human subjects exposed to a mean formaldehyde concentration of 0.26 mg/m^3 during the work day compared with a referent group exposed to 0.09 mg/m^3. The critical effects in this study included nasal obstruction and discomfort, lower airway discomfort, and eye irritation. A NOAEL and a LOAEL may be derived from these data but no other dose-response information was provided. This study included only adults, but there is evidence that children may be more susceptible to long term exposures to formaldehyde than are adults. Thus, in the absence of child-specific data, an intraspecies uncertainty factor of 10 for toxicodynamic variability and developmental susceptibility was applied.

Table 3. CAL-OEHHA 8-hr REL: Key Study and Decision Points

Study	Wilhelmsson and Holmstrom, 1992
Study population	66 chemical plant workers
Exposure method	Discontinuous occupational exposure
Exposure continuity	8 hr/day, 5 days/week (assumed)
Exposure duration	10 years (average); range 1-36 years
Critical effects	Nasal obstruction and discomfort, lower airway discomfort, and eye irritation.
LOAEL	Mean 0.26 mg/m^3 (range 0.05 – 0.6 mg/m^3) (described as exposed group)
NOAEL	Mean of 0.09 mg/m^3 (described as control group of office workers)
Benchmark concentration	not derived
Time-adjusted exposure	0.09 mg/m^3 (time adjustment not applied)
Human Equivalent Concentration	not applied
LOAEL uncertainty factor (UF_L)	1 (NOAEL observed)
Subchronic uncertainty factor (UF_S)	not applied
Annimal Toxicokinetic ($UF_{A\text{-}K}$)	1 (default, human study)
Annimal Toxicodynamic ($Uf_{A\text{-}d}$)	1 (default, human study)
Human Toxicokinetic ($UF_{H\text{-}K}$)	1 (site of contact; no systemic effects)
Human Toxicodynamic ($UF_{H\text{-}d}$)	10 (asthma exacerbation in children)
Cumulative uncertainty factor	10
Reference Exposure Level	9 μg/m^3 (7 ppb)

TCEQ Reference Value (ReV)

TCEQ 24-hr ReV (proposed) of 30 µg/m³ was derived from a NOAEL of 0.09 mg/m³ identified by Wilhelmsson and Holmstrom (1992).

Parameter	Summary
Study	Wilhelmsson and Holmstrom (1992)
Study population	66 exposed workers, 36 controls
Study quality	high
Exposure Methods	0.26 mg/m^3 for workers 0.09 mg/m^3 for controls
Critical Effects	elevated rates of symptoms such as eye, nasal, and lower airway discomfort
POD_{oc} (NOAEL)	0.09 mg/m3
Exposure Duration	5 days per week, 10 years (mean)
Extrapolation to 24-hr	Not applicable
24-hr POD_{HEC}	0.09 mg/m3
Total UFs	3
Interspecies UF	Not applicable
Intraspecies UF	3
LOAEL UF	Not applicable
Database UF *Database Quality*	1 High
Acute 24-hr ReV Acute 24-hr AMCV	30 $\mu g/m^3$ (24 ppb)

Selected excerpts from TCEQ (2014) follow:

3.3 Critical Effect and Point of Departure

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

3.4 Duration Adjustments

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

3.5 Uncertainty Factors

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

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

A UF_H of 3 was selected since although the study included potentially sensitive subgroups (i.e., atopics, those with a positive skin reaction), there is a potential for a healthy worker effect (i.e.,

sensitive workers could have left the formaldehyde-exposed group), and the scientific literature indicates a broad range of reported human susceptibility to the irritating properties of airborne formaldehyde (ACGIH 2001).

TCEQ also developed a 1-hr ReV at 50 µg/m³ (TCEQ, 2008). TCEQ based their ReV on Pazdrak et al. (1993), previously discussed above (see ATSDR Acute Minimal Risk Level of 50 µg/m³). A second study by Krakowiak et al. (1998) was also used where 20 volunteers were exposed to 0.5 mg/m3 (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. RESULTS: 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 FEV1, PEF, or PC20H values in healthy or asthmatic subjects due to formaldehyde exposure, although the baseline FEV1 and PEF values for healthy and asthmatic subjects differed. Formaldehyde did not increase the bronchial response to histamine (PC20H) 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.

Choice of Acute ITSL

ATSDR and TCEQ used the Pazdrak (1993) study to identify the 0.4 ppm exposure dose for the derivation of acute screening levels of 50 µg/m³ for both agencies. However, ATSDR applied an averaging time that is defined as “up to 14 days”, whereas TCEQ defined their acute ReV averaging time as a 1-hr.

Both TCEQ 24-hr ReV of 30 µg/m³ and CAL-OEHHA 8-hr REL of 9 µg/m³ were derived from a NOAEL of 0.09 mg/m³ identified in Wilhelmsson and Holmstrom (1992), an occupational study which had a 10-yr average exposure period (range 1 to 36 years). Exposures were likely 8-hrs per day (a typical work-shift) which allowed for recovery during off-hours and weekends. Both agencies did not make duration-adjustments because the benchmarks were derived from a 10-year repeated dose study which indicates that irritation appears to be concentration dependent rather than duration dependent. The LOAEL of 260 µg/m³ found in the Wilhelmsson and Holmstrom (1992) study is lower than the LOAEL identified in the Pazdrak et al., (1993) study of 500 µg/m³ (2-hour exposure), which was used by ATSDR to derive the MRL of 50 µg/m³. Pazdrak et al. (1993) did not identify a NOAEL. Deriving an acute ITSL from the NOAEL found by Wilhelmsson and Holmstrom (1992) would provide protection both in the short- and

long-term time periods similar to typical exposure scenarios (e.g., intermittent and long-term) encountered around an industrial facility permitted to emit formaldehyde.

The only difference in derivation of health based screening levels between the TCEQ ReV of 30 ug/m³ and the Cal-OEHHA REL of 9 µg/m³ was in the magnitude of the intrahuman uncertainty factor. TCEQ used the default intraspecies UF of 3 whereas Cal-OEHHA used a human toxicodynamic UF (UF_{H-d}) of 10 in order to protect against the possibility of asthma exacerbation in children. Cal-OEHHA reasoned that a 10 fold uncertainty factor was warranted because:

> This study included only adults, but there is evidence that children may be more susceptible to long term exposures to formaldehyde than are adults. Thus, in the absence of child-specific data, an intraspecies uncertainty factor of 10 for toxicodynamic variability and developmental susceptibility was applied.

Cal-OEHHA (2008) also referenced California Health and Safety Code, Section 39669.5(c) as rationale for their conclusion that formaldehyde, "may disproportionately impact children." The study population evaluated in Wilhelmsson and Holmstrom (1992) specifically included "atopic" individuals (i.e., individuals that are allergic as identified by IgE antibodies to formaldehyde and via epicutaneous test with 1% formaldehyde solution). Standard risk assessment methodology includes applying an UF for sensitive subpopulations that can be either 3 or 10 depending on the known or expected variability of response in the human population. The authors analyzed whether atopic individuals were more or less likely to have irritation symptoms when exposed to formaldehyde. They found that atopics were no more likely to suffer from hyperreactivity as non-atopics. In other words, persons normally thought to be a sensitive subgroup (as identified as "atopic") react the same to formaldehyde exposure as the general population. This indicates that the human population is less variable in response to formaldehyde. Consequently, a decrease of the UF for sensitive subpopulations from 10 to 3 was deemed appropriate. Therefore, the MDEQ-AQD will use the TCEQ-ReV of 30 µg/m³ as the basis for the ITSL. It is conceivable that on a short term basis ambient air concentrations of formaldehyde could exceed 30 µg/m³ during a 24-hr exposure. However, since the irritation effects of formaldehyde are more dependent on concentration than duration, an ITSL of 30 µg/m³ with 24-hr averaging time may be expected to be protective for adverse health effects from somewhat higher formaldehyde concentrations over shorter lengths of time.

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Appendix A. Graphical Representation of Health Benchmarks for Formaldehyde