MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Chlorine (CAS# 7782-50-5)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: Review of an Acute Initial Threshold Screening Level for Chlorine (CAS# 7782-50-5)

SUBJECT: June 6, 2011

The acute Initial Threshold Screening Level (ITSL) for chlorine is 500 ug/m^3 based on an 8-hour averaging time. This acute ITSL is derived as a short-term exposure and will be used in conjunction with the ITSL derived for chlorine in the memo dated November 1, 2010. The averaging time for the chlorine ITSL in the November 1, 2010 memo will be changed from 0.3 µg/m^3 based on a 24-hour averaging time to 0.3 µg/m^3 based on an annual averaging time to ensure protection from long-term exposure and health risks in conjunction with the acute ITSL's protection from short-term peak exposures. For information on the derivation of the 0.3 µg/m^3, please refer to the November 1, 2010 memo to the file for chlorine.

After an extensive literature review was conducted to determine the November 1, 2010 ITSL for chlorine, a further review of acquired information was conducted to determine the acute ITSL. The Agency for Toxic Substances and Disease Registry (ATSDR) drafted a Toxicological Profile for Chlorine in September 2007, which determined an acute Minimal Risk Level (MRL) for chlorine gas inhalation of 0.07 ppm. The studies of greatest relevance for determining an acute ITSL are described below.

The study by Anglen (1981) exposed 29 male and female volunteers to concentrations of 0, 0.5, 1, or 2 ppm chlorine for either 4 or 8 hours. Sensations were recorded before and during exposure, and pulmonary function was monitored by measuring forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), expiratory flow rate at 50 percent of FVC (EFR50), total lung capacity (TLC), and expiratory flow rate between 25 and 75 percent of FVC (EFR25-75) before and during exposure. While in the exposure chamber, each subject exercised for 15 minutes out of each hour. Exercise was done using either an inclined treadmill or a step test to attain a heart rate of approximately 100 beats per minute, which has been defined by the American Industrial Hygiene Association as light to moderate work. Each subject's heart rate was determined and recorded before and after each exercise period. Itching and burning of the throat were the highest responses and were most prevalent by the end of an 8-hour exposure to 1 ppm chlorine. Responses for sensations of itching or burning of the nose, runny nose, and itching or burning of the eyes were also prevalent after an 8-hour exposure to 1 ppm chlorine. Overall, males had stronger irritation responses than females. Exposure to 1 or 2 ppm chlorine for 8 hours produced significant changes in pulmonary function, but similar exposures to 0.5 ppm did not. Exposure to 2 ppm for up to 30 minutes produced no increase in subjective irritation and exposure to 2 ppm for 2 hours did not alter pulmonary function.

The study by Rotman et al., (1983) exposed 8 healthy male volunteers to concentrations of 0, 0.5, or 1 ppm chlorine for 8 hours. Pulmonary function measurements were conducted pre-exposure, during exposure at 4 hours, after 8 hours exposure, 2 hours post-exposure, the next day. During exposure, the subjects exercised on a treadmill for 15 minutes each hour on an inclined treadmill or by a simple step test to stimulate light-to-moderate work that raised the heart rate to 100 beats per minute. Specific respiratory parameters measured included FVC, FEV_1, forced expiratory volume in 1 second as %FVC (FEV_1%), peak expiratory flow rate (PEFR), forced expiratory flow rate at 50 and 25% vital capacity (FEF_{50} and FEF_{25}, respectively), TLC, expiratory reserve volume (ERV), functional residual capacity (FRC), residual volume, airway resistance (Raw), single-breath diffusing capacity for carbon monoxide (LD_{co}), closing volume, and difference in nitrogen concentrations between 750 and 1,250 ml of inhaled vital capacity (ΔN_2). Exposure to chlorine caused runny nose and mild burning in the throat, but no such effects were reported at 0.5 ppm. Significant changes in pulmonary function tests were mostly observed at the 1.0 ppm exposure level and were evident after 4 hours of exposure. Changes were observed in FEV_1, PEFR, FEF_{50}, FEF_{25}, TLC, Raw, and ΔN_2. Larger changes were seen in some of the above parameters after 8 hours of exposure. Few of the changes were still evident 24 hours after exposure and most of the parameters had returned to pre-exposure values by that time. One of the volunteers with a history of allergic rhinitis experienced severe distress during exposure, and shortness of breath and wheezing caused him to exit the chamber before the full 8-hour exposure to 1 ppm.

The Anglen dissertation and Rotman et al., study have very similar research methods. D. M. Anglen is one of the authors in the Rotman et al., study. This similarity should be noted. It is unclear if they report different experiments, or if they report somewhat differently on the same experiments. The Rotman study does reference the Anglen dissertation and discusses the similarities and differences in findings in discussion section. In general both studies support a NOAEL of 0.5 ppm for chlorine for an 8 hour exposure.

A study by D'Alessandro et al. (1996) evaluated pulmonary function in male and female volunteers aged 18 to 50 years: 10 volunteers with and 5 volunteers without airway hyperreactivity (HR, defined by baseline methacholine hyperresponsiveness). The HR volunteers were exposed to 0.4 ppm or 1.0 ppm chlorine and the healthy volunteers were exposed to 1.0 ppm chlorine. All exposures were 60 minutes in duration. Airflow and airway resistance were measured immediately before and immediately after exposure. Also, lung volumes, airflow, diffusing capacity, airway resistance, and responsiveness to methacholine were measured 24 hours before and 24 hours after exposure. Exposure of the HR group to 0.4 ppm chlorine resulted in no significant change in airflow or resistance either immediately or 24 hours after exposure. Exposure to 1.0 ppm chlorine resulted in an immediate decrease in FEV1 and FEF25-75% and increase in airway resistance among normal and HR subjects. Twenty-four hours after exposure, there were no significant changes for healthy or HR subjects in airflow, lung volumes, diffusing capacity, resistance, or methacholine responsiveness. This study shows support for the above studies, but due to the short exposure time, it was not chosen as the key study for acute ITSL derivation.

A study by Schins et al. (2000) evaluated eight volunteers to chlorine 6 hours per day on 3 consecutive days to each of the four exposure conditions, 0, 0.1, 0.3, and 0.5 ppm chlorine. Pulmonary function including effort-dependent parameters and effort-independent parameters were evaluated before and after exposures. In addition, nasal lavage measurements were performed before and after each exposure and 1 and 4 days after each exposure. The nasal lavage fluid was examined for total cells, epithelial cells, neutrophils, lymphocytes, eosinophils, monocytes, albumin (an indicator or epithelial permeability), and interleukin-8 (indicator of inflammatory response). Complaints by the volunteers were judged to be non-treatment related. Examination of the nasal lavages gave no indication of an inflammatory response or irritant effects on the nasal epithelium. The results of the pulmonary function tests showed that the

only significant effect related to chlorine exposure was a difference in maximal mid expiratory flow (MMEF) between 0 and 0.5 ppm exposure; but this was attributed to an unexplained shift in baseline values during control exposure (0 ppm). This makes this study of questionable value for risk assessment purposes.

Another study by Schusterman et al., (2003) measured nasal airway resistance in 52 healthy adults (24 males and 28 females) before and after exposure to 0 or 1 ppm chlorine for 15 minutes. Subjects were separated by age (18-34, 35-51, 52-69 years), gender, and allergic rhinitis (27 were positive) status. Nasal airway resistance was measured by active posterior rhinomanometry. Exposures to air and chlorine were a week apart. A subject with allergic rhinitis showed a significantly greater increase in nasal airway resistance (49% increase from baseline) than healthy subjects (10% increase from baseline) 15 minutes after exposure. The increase in nasal airway resistance was most pronounced in older subject and least pronounced in the youngest group. No significant differences were seen between males and females. This study also supports the other studies, but due to the short exposure time, was not the key study used for deriving an acute ITSL.

Together, the above studies provides evidence that exposure to chlorine causes sensory irritation such as itching and burning of the throat, nose, and eyes at 1 ppm (Anglen; Rotman), runny nose at 1 ppm (Anglen; Rotman), and itchy eyes at 1 ppm (Rotman) for up to 8 hours/day. Chlorine exposure can also cause pulmonary changes such as: decrease in FVC (Rotman), decrease in FEV_1 (Rotman; D'Alessandro), decrease in FEF 25-75% (D' Alessandro), Increase in TLC and FRC (Rotman), and increase in airway resistance (D'Alessandro; Schins) after exposure to 1 ppm chlorine for up to 8 hours/day. These changes were not found in the volunteers exposed to 0.5 ppm chlorine.

The acute ITSL for chlorine is based on the Anglen (1981) and Rotman et al., (1983) studies which reported 0.5 ppm as a NOAEL for 8 hours/day for sensory irritation and pulmonary function. The Anglen (1981) and Rotman et al., (1983) studies exposed their volunteers in ppm. To determine an ITSL for chlorine the values must be changed to ug/m^3. Equation 4-1b on page 4-20 in EPA (1994) was used to convert the doses with the assumptions that the testing was performed at 25°C and 760 mmHg, that 1 g-mole of a perfect gas occupies 24.45 L.

$$mg/m^3 = \frac{ppmxMW}{24.45}$$

The molecular weight of chlorine gas is 70.906 g/mol. Using the equation above:

$$mg/m^3 = \frac{0.5\,ppm \times 70.906\,{}^{g}\!/_{mol}}{24.45} = 1.45002045\,{}^{mg}\!/_{m^3} = 1{,}450\,{}^{\mu g}\!/_{m^3}$$

Based on the above studies with human volunteers, 8 hours was the longest period of exposure for which there is information. Several of the studies listed above contained volunteers who were tested at the NOAEL range and showed no ill effects, but the small number of sensitive individuals does not ensure adequate protection for sensitive individuals in a population. Therefore, consistent with ATSDR (2007) an uncertainty factor of 3 is applied to account for sensitive individuals.

$$ITSL = \frac{1{,}450\,{}^{\mu g}\!/_{m^3}}{3} = 483.3\,{}^{\mu g}\!/_{m^3} \ldots roundedtoonesignificantfigure = 500\,{}^{\mu g}\!/_{m^3}$$

According to R 336.1229(2) (b) in part 2 page 60 of Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of

Environmental Quality, the initial threshold screening level shall be determined by any alternative methodology to assess noncarcinogenic health effects that can be demonstrated to the department to be more appropriate based on toxicological grounds and that is supported by the scientific data. The acute ITSL is based on supporting data from five studies, two of which have 8 hour inhalation data obtained by human volunteers and with the addition of an uncertainty factor to account for sensitive populations.

Therefore, the acute Initial Threshold Screening Level (ITSL) for chlorine is 500 ug/m^3 based on an 8 hour averaging time. This acute ITSL is derived as a short-term exposure and will be used in conjunction with the ITSL derived for chlorine in the memo dated November 1, 2010. The averaging time for the chlorine ITSL in the November 1, 2010 memo will be changed from 0.3 µg/m^3 based on a 24-hour averaging time to 0.3 µg/m^3 based on an annual averaging time. For information on the derivation of the 0.3 µg/m^3, please refer to the November 1, 2010 memo to the file for chlorine.

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MICHIGAN DEPARTMENT OF NATURAL RESOURCES & ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: File for Chlorine (CAS# 7782-50-5)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: November 1, 2010

SUBJECT: Review of Screening Level for Chlorine (CAS# 7782-50-5)

The Initial Threshold Screening Level for chlorine is 0.3 µg/m^3 based on a 24-hour averaging time.

A literature review was conducted to determine an initial threshold screening level (ITSL) for chlorine. The following references and databases were searched to derive the above screening level: EPBCCD, Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV)/Biological Exposure Indices (BEI) 2004 guide, DEQ library, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, CAS Online, National Library of Medicine (NLM)-online, Environmental Protection Agency (EPA) Aggregated Computational Toxicology Resource (ACToR) Database, Agency for Toxic Substances and Disease Registry (ATSDR) database, Kirk-Othmer chemical encyclopedia, and Patty's Industrial Hygiene & Toxicology.

$$Cl - Cl$$

Chlorine (CAS# 7782-50-5) has a formula of Cl_2 and a molecular weight of 70.91 g/mol, it is a yellow/green gas that is highly reactive and therefore generally will not exist in this form for very long in the environment. Large releases of chlorine gas have occurred during transport by train and in chemical processing causing exposure to workers and local residents as the gas are heavier than air and will stay close to the ground. Chlorine gas is used as an oxidizing agent in water treatment and chemical processes; used to disinfect swimming pool water, and used to bleach wood pulp in pulp mills. Chlorine can be released from sodium hypochlorite, which is commonly used as a household cleaner and disinfectant. Chlorine is a direct acting irritant and exposure results in irritation of the respiratory tract, eyes, and skin. Chlorine may exacerbate asthma since it is a powerful respiratory irritant. Chlorine is a federal hazardous air pollutant (HAP). See http://oehha.ca.gov/air/toxic_contaminants/pdf_zip/chlorine_final.pdf.

The effect of chlorine depends on how much chlorine are present, the exposure, and the length of exposure. "The following effects have been observed in humans briefly exposed to chlorine: mild nose irritation at 1-3 ppm; eye irritation at 5 ppm; throat irritation at 5-15 ppm; immediate chest pain, vomiting, changes in breathing rate, and cough at 30 ppm; lung injury (toxic pneumonitis) and pulmonary edema (fluid in the lungs) at 40-60 ppm; death after 30 minute exposure at 430 ppm; death after a few minute exposure at 1,000 ppm" (ATSDR, 2008). Children have been exposed to chlorine gas leaking from tanks while they were in swimming pools. There is some concern with competitive swimmers inhale and micro aspirate large amounts of air near the water surface, which exposes them to chlorine from off-gassing of swimming pool disinfectants.

Animals also have been studied for occurrence of adverse effects. A two-year inhalation exposure study of chlorine in B6C3F1 mice and F344 rats by Wolf DC et al., 1995, groups of 70 each of female and male mice and male rats were exposed to 0, 0.4, 1.0, or 2.5 ppm chlorine gas for 6 hours/day, 5 days/week or 3 days/week for female rats for two years, with an interim necropsy of 10 rats/sex/concentration group at 12 months. The reduced exposure of female rats was based on unpublished data from the investigators that showed female rats to have a greater sensitivity to repeated long-term exposure to chlorine. Exposure dependent lesions were confined to the nasal passages in all sex and species groups. Chlorine-induced lesions, which were most severe in the anterior nasal cavity, included respiratory and olfactory epithelial degeneration, septal fenestration, mucosal inflammation, respiratory epithelial hyperplasia, squamous metaplasia, and goblet cell hypertrophy and hyperplasia, and secretory metaplasia of the transitional epithelium of the lateral meatus. Intracellular accumulation of eosinophilic proteinaceous material was also a prominent response involving the respiratory, transitional, and olfactory epithelia, and in some cases the squamous epithelium of the nasal vestibule. Many of these nasal lesions exhibited an increase in incidence and/or severity that was related to chlorine exposure concentration and were statistically significantly increased at all chlorine concentrations studied. In this study, the incidences were presented as percentages of all animals for which the nasal passages were adequate for microscopic examination, but the number of animals examined were not provided (ATSDR, 2007; Wolf, DC, 1995).

A one-year inhalation toxicity study of chlorine in Rhesus monkeys by Klonne DR. et al., 1987, was a chronic inhalation exposure study using male and female rhesus monkeys (4/sex/exposure level) exposed to either; 0, 0.1, 0.5, or 2.3 ppm chlorine for 6 hours/day, 5 days/week, for one year. Pulmonary diffusing capacity of CO and distribution of ventilation, body weights, urinalysis, EKG, hematology, and clinical chemistry were evaluated monthly during the study. At study termination, the heart, lungs, trachea, liver, gonads, kidneys, spleen, and brain were weighed and histological evaluations were performed. The nasal tissues (at the first palatine ridge just posterior to the third, fifth, and seventh palatine ridges), trachea, and lungs were also examined (ATSDR, 2008; Klonne DR, 1987). The study by Klonne et al., 1987 the 2.3 ppm exposure group showed conjuctival irritation (tearing, reddened eyes, and rubbing of the eyes) after six weeks of exposure and at termination showed irritation of the conjunctiva, but no other gross changes in the eye. The only treatment-related effects consisted of minimal nasal epithelial hyperplasia characterized by increased cell numbers and loss of cilia and goblet cells in the respiratory epithelium of the nose and trachea. In some cases, the hyperplasia was associated with mild suppurative inflammatory response. The lowest exposure concentration of 0.1 ppm chlorine is considered a LOAEL for nasal lesions in monkeys (ATSDR, 2008).

Ibanes et al. (1996) re-examined the respiratory tissues from the chronic studies in monkeys, rats, and mice summarized above to better characterize the lesions and to improve human risk assessments based on these data sets. In general, the re-evaluation found a good correlation between the subjective scores of tissue responses on the original studies and quantitative analyses in the re-evaluation. In the Wolf et al., (1995) study, based on the increased incidence of various types of lesions in the nasal passages, the exposure level of 0.4 ppm constitutes a LOAEL for respiratory effects in rats and mice (minimal to moderate alterations in the nasal epithelium); a NOAEL was not defined. In the Klonne et al., (1987) study, the lowest exposure concentration of 0.1 ppm chlorine is a LOAEL for nasal lesions (minimal nasal epithelial hyperplasia) in monkeys (ATSDR, 2007). In both studies, the upper respiratory tract was the target for chlorine toxicity. In general, lesions were less severe in monkeys than in rats and mice, but extended more distally in the respiratory tract. For the most part in mice and rats, the nasal lesions were site specific, but the severity and/or incidence were not always concentration-dependent. Rats and mice are obligatory nose breathers with greater surface

area-to-volume ratio of the upper respiratory tract than primates. Therefore, exposure of rodents and primates to equal concentrations for equal amounts of time will likely result in greater pathological changes in the nasal area of the rodent (Barrow et al., 1979).

Although primates appear to be a better model to evaluate potential respiratory effects in humans than rodents, the primate study exposure was only for a year and given that the lifespan of rhesus monkeys in a laboratory environment is 30 years this study is not long enough to assess lifetime exposure risk assessment for chlorine. ATSDR used the Klonne et al., (1987) study as the basis for derivation of a chronic-duration inhalation MRL for chlorine (ATSDR, 2008). California EPA used the Wolf et al., (1995) study to derive their chronic REL, as the mouse study was performed for 2 full years (the expected lifetime of rodents). California EPA also noted that the samples sizes were large at 70 animals per dose group for each sex. Based on these considerations the decision was made to use the Wolf et al., study to perform our risk assessment.

Chlorine is a highly reactive gas which combines quickly with water and anything else it comes in contact with and is not generally found in the environment unbound. According to EPA 1994, chlorine can be classified as a category 1 gas as it is rapidly reactive and highly water soluble as per figure 3-9 on page 3-37. Since chlorine exposure caused nasal lesions and irritation of the nasal epithelium with the trachea showing lesser irritation, chlorine is considered to have the greatest effect in the extrathoracic (ET) region. The EPA 1994 ET regional gas dose ratio ($RDGR_{ET}$) equation 4-18 on page 4-47 was used to calculate chlorine's effect on the nasal epithelium.

$$RGDR_{ET} = \frac{(Dose_{ET})_A}{(Dose_{ET})_H} \cong \frac{(\frac{\dot{V}_E}{SA_{ET}})_A}{(\frac{\dot{V}_E}{SA_{ET}})_H}$$

Where:

V_E = minute volume (L/min = cm^3/min)
SA_{ET} = surface area of the extrathoracic region (cm^2) and
A, H = subscripts denoting laboratory animal and human, respectively.

To calculate the minute volume [V_E = tidal volume (V_T) x breathing frequency (f)] are calculated using an allometric scaling equation provided by the US EPA 1994. The general form of this equation is:

$$\ln(\dot{V}_E) = b_0 + b_1 \ln(BW)$$

Where b_0 is the intercept and b_1 is the coefficient values used to calculate default minute volumes based on body weight found in Table 4-6 on page 4-29 in EPA 1994 and BW is body weight in kg. The average body weight of the male F344 rat is 0.38 kg (EPA, 1988). Therefore,

$$\ln(\dot{V}_E) = -0.578 + 0.821\ln(0.38kg)$$
$$\ln(\dot{V}_E) = -0.578 + (-0.7944)$$
$$\dot{V}_E = e^{1.372} = 0.2535\,{}^{L}\!/_{\min}$$

The default V_E for human is 13.8 L/min based on an average body weight of 70 kg and default breathing frequency of 20m^3/day (EPA, 1994). The RGDR equation above requires surface area values for humans and rats. Default surface area values for respiratory effects for humans were taken from table 4-4 on page 4-26 in EPA 1994. The extrathoracic respiratory surface area is 200 cm^2 for humans. The surface area for rats is 15.0 cm^2. Therefore, the default $RGDR_{ET}$ for rat to human is:

$$RGDR_{ETrat/human} = \frac{(Dose_{ET})_{rat}}{(Dose_{ET})_{human}} = \frac{(\frac{\dot{V}_E}{SA_{ET}})_{rat}}{(\frac{\dot{V}_E}{SA_{ET}})_{human}} = \frac{(\frac{0.2535\,{}^{L}\!/_{\min}}{15cm^2})}{(\frac{13.8\,{}^{L}\!/_{\min}}{200cm^2})} = 0.2449$$

The Wolf study exposed B6C3F1 mice and F344 rats, both male and female (70/sex/exposure level) to either; 0, 0.4, 1.0, or 2.5 ppm for 6 hours/day, 5 days/week, or 3 days/week for female rats (as the authors observed the females to be more sensitive than males) for two years. Both male and female mice and rats showed upper respiratory epithelial lesions after exposure to chlorine including: septal fenestration, squamous epithelium hyperplasia, squamous epithelium eosinophilic proteinaceous accumulation, respiratory epithelium hyperplasia, respiratory epithelium eosinophilic proteinaceous accumulation, squamous metaplasia, olfactory epithelium atrophy, and olfactory epithelium eosinophilic proteinaceous accumulation.

The United States Environmental Protection Agency Benchmark Dose Software (BMDS) version 2.1.2 was used to determine an IRSL using a Benchmark Dose Response of 10% (BMR_{10}), which is a default value in the software. The software was run using dichotomous data utilizing the following models: Gamma, Logistic, Log Logistic, Log Probit, Multistage, Probit, Weibull, and Quantal-Linear. For chlorine, the BMDS software calculated the best fit for Multistage and Log Logistic models. After running all the above lesions for both male and female mice and rats, the model with the best goodness of fit p value was the Log Logistic model for chlorine exposed male rat respiratory epithelium eosinophilic proteinaceous accumulation (the results of the benchmark dose runs are an appendix to this document). The BMDL for the Log Logistic model was 0.082279 ppm.

The Wolf study exposed their subjects in ppm. To determine a benchmark dose response the concentrations must be converted to mg/m^3. Equation 4-1b on page 4-20 in EPA (1994) was used to convert the doses with the assumptions that the testing was performed at 25°C and 760 mmHg, that 1 g-mole of a perfect gas occupies 24.45 L.

$$mg/m^3 = \frac{ppmxMW}{24.45}$$

The molecular weight of chlorine gas is 70.906 g/mol. Therefore, the BMDL for the Log Logistic model was used in place of the ppm value below:

$$mg/m^3 = \frac{0.082279\,ppmx70.906g/mol}{24.45} = 0.2386mg/m^3$$

Since the inhalation study was performed in animals using discontinuous exposure regimens, the listed conversion factors used in determining the adjusted dose to reflect a benchmark level for continuous exposure. The following equation is based on equation 4-2 on page 4-21 of EPA, 1994.

$$BMDL_{10[adj]}(^{mg}/_{m^3}) = BMDL_{10}(^{mg}/_{m^3}) \times \frac{6hrs}{24hrs} \times \frac{5days}{7days}$$

$$BMDL_{10\{adj\}}(^{mg}/_{m^3}) = 0.2386\,^{mg}/_{m^3} \times \frac{6hrs}{24hrs} \times \frac{5days}{7days} = 0.04261\,^{mg}/_{m^3}$$

The human equivalency concentration (HEC) is determined below for male rat respiratory epithelium eosinophilic proteinaceous accumulation. The following equation is based on equation 4-3 on page 4-25 in EPA, 1994.

$$BMDL_{10[HEC]}(^{mg}/_{m^3}) = BMDL_{10[adj]}xRGDR_{ET(rat/human)} = 0.04261\,^{mg}/_{m^3} \times 0.2449 = 0.01044\,^{mg}/_{m^3}$$

$$BMDL_{10[HEC\}}(^{mg}/_{m^3}) = 0.01044\,^{mg}/_{m^3} = 10.44\,^{\mu g}/_{m^3}$$

Uncertainty factors must be applied to account for recognized uncertainties in extrapolating experimental conditions to estimate a human scenario. The application of an uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustment and an uncertainty factor of 10 for human variability was used to determine a screening level calculating by RfC methodology. The following equation is based on Equation 4-50 on page 4-74 in EPA, 1994 was used to calculate an inhalation reference concentration.

$$RfC = \frac{BMDL_{10[HEC]}}{UF} = \frac{10.44\,^{\mu g}/_{m^3}}{(10 \times 3)} = 0.3479\,^{\mu g}/_{m^3} \ldots rounded \ldots to \ldots one \ldots significant \ldots figure \ldots 0.3\,^{\mu g}/_{m^3}$$

According to R 336.1232(1) (a) in part 2 page 64 of Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality, the ITSL for chlorine equals the inhalation RfC if the inhalation RfC can be determined from the best available information sources. Therefore, the ITSL for chlorine is 0.3 µg/m^3 based on a 24-hour averaging time.

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