Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the June 2016 Proposed Chlorine Development Support Document

The Development Support Document (DSD) for chlorine was proposed in June 2016. Olin™ and the American Chemistry Council (ACC) submitted comments on the proposed DSD. The TCEQ appreciates the effort put forth to provide comments on this proposed DSD for chlorine. The goal of the Toxicology Division and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. Substantive comments were divided into sections and are provided below, followed by TCEQ responses.

Olin™ Comments

This company provided a general discussion of various comments followed by the specific, enumerated comments. The substantive comments relevant to the derivation of toxicity factors are summarized and addressed by the TCEQ below.

Comment No. 1:

Apply a hazard quotient (HQ) of 0.75 instead of 0.3, given the short atmospheric half-life of chlorine and the low severity and reversibility of the site-of-contact irritation effects on nasal mucosa.

Based on the TCEQ guidance (2006, 2015), the application of an HQ of 0.3 allows for the potential existence of several sources of the chemical under consideration ('cumulative and aggregate exposure'), with an expectation that total air values would not exceed an overall HQ of 1. This approach is a conservative one that supports the guidance's goal of 'no significant risk'. However, such an additional 3-fold extra conservatism is not needed in the case of chlorine for several reasons, including its atmospheric reactivity and resultant short half-life and the less severe, reversible nature of the toxic lesion.

a) As stated above, the reactive chemical chlorine has a very short half-life in air (atmospheric t½ <2-4 h according to ECHA IUCLID). Thus any chlorine present from other sources will also be very short-lived, leaving little or no possibility for a cumulative or aggregate effect to necessitate the additional 3-fold safety factor. Using an HQ of 0.75 would be supported by the very short atmospheric half-life of chlorine and meets the guidance goals of an overall HQ <1.
b) The critical effect identified for long-term exposure to chlorine gas is nasal lesions, identified as the 'combined incidences of hyperplasia in the nasal epithelium with loss of goblet cells and cilia,' (TCEQ, 2016) in male and female monkeys following 1 year of inhalation exposure to chlorine. The incidence of these nasal lesions was 'mild concentration-related respiratory epithelial hyperplasia with focal loss of cilia over the range of concentrations tested (0, 0.1, 0.5, and 2.3 ppm)'. Nasal lesions such as those identified in the chronically exposed monkeys are considered not to be a severe effect;

indeed they were defined as 'mild'; in addition, typically such nasal lesions are reversible once exposure ceases (see Brandenberger et al., 2015). Thus, protecting against both a non-severe and a reversible effect offers more flexibility in the determination of appropriate conservatism vis-à-vis a target for HQ.

TCEQ Response:

The TCEQ appreciates these comments by Olin™. However, an environmental half-life of several hours (i.e., "atmospheric t½ <2-4 h according to ECHA IUCLID") is more than enough time for off-site impacts to occur and combine with those from other sources. Even if emissions were from a non-continuous source and the half-life were 1 hour, it would take approximately 5 hours for the resulting chlorine concentration(s) to essentially be eliminated entirely. At 1 hour and average wind speed, the persisting concentrations resulting from emissions could be many miles away, combined with emissions from any other sources impacting the area. Finally, it is noted that there would be no routine chlorine monitoring to confirm the protectiveness of the proposed HQ of 0.75.

Additionally, the TCEQ ReVs and ESLs are appropriately based on mild adverse effects. Severe and/or irreversible effects are not generally used to develop toxicity factors intended to be protective against the most sensitive effects. As such, the TCEQ guidelines intend to apply a factor of 0.3 to ReV values based on mild effects, as is the case with chlorine. Finally, it is simply noted that reversibility arguments are not relevant to chronic ReVs (or the HQ factor applied to them) since they are derived to be protective of *continuous* lifetime exposure (i.e., without the opportunity for reversibility due to the lack of exposure).

In summary, the TCEQ does not find the short half-life in air or mild adverse effect arguments for a higher HQ compelling and a factor of 0.3 continues to be applied to the chronic ReV in the final DSD.

Comment No. 2:

Apply selected Uncertainty Factors (UF) to the POD_{adj} based on available information:

Given the reliance on monkey data to determine the $^{chronic}ESL_{threshold(nc)}$ for chlorine, and both the physiological similarity in nasal passages between humans and non-human primates and the expectation that a reactive chemical like chlorine will exert its toxic effects via the same mode-of-action for a site-of-contact effect in monkeys as in humans, TCEQ should consider reducing the UF used to account for potential species differences in toxicodynamics from three (3) to one (1), similar to the UF applied for differences in toxicokinetics.

TCEQ Response:

After careful consideration, the TCEQ concurs with this comment and has added additional discussion to the DSD to support a UF_A of 1 for the chronic assessment, which relies upon a Rhesus monkey study.

Comment No. 3:

Chlorine gas is understood to dissolve in aqueous tissue upon inhalation, resulting in the formation of HCl and HOCl, from which the irritating effects are believed to stem. Thus comparison of the proposed $^{chronic}ESL_{threshold(nc)}$ for Cl_2 with the one set for HCl by TCEQ (2015) is important since the effects driving both these $^{chronic}ESL_{threshold(nc)}$ values are nasal/upper respiratory irritation. The 2015 $^{chronic}ESL_{threshold(nc)}$ value for HCl is 5.4 ppb, which is 135-fold higher than the $^{chronic}ESL_{threshold(nc)}$ currently proposed for Cl_2, despite the fact that both are based on nasal/upper respiratory irritation, in the case of Cl_2 apparently caused by HCl + HOCl derived from Cl_2. It is not clear why there should be such a large discrepancy between these two values, although it is perhaps reasonable to consider a factor of two reduction in comparing the HCl value for Cl_2 due to the presence of two chlorine atoms in Cl_2 and thus twice the capacity for formation of HCl and perhaps twice the subsequent irritation on a molar basis. Thus one might expect a value in the range of 2.7 ppb for the Cl_2 $^{chronic}ESL_{threshold(nc)}$, using that simple comparative approach.

TCEQ Response:

The TCEQ acknowledges the similarity in MOA for Cl_2 and HCl and the resulting expectation that the respective toxicity factors should perhaps not be multiple orders of magnitude apart. Given the relatively insignificant contribution of H to the molecular weight of HCl, the toxicity factors for both compounds are essentially for chlorine (e.g., µg chlorine/m^3 air), albeit in different parent chemical forms. The TCEQ has more carefully evaluated results from the key Rhesus monkey study (Klonne et al. 1987) as to adversity and identified a LOEL of 0.5 ppm as the POD. After duration adjustments and with the revised total UF of 30 (UF_H of 10, UF_{Sub} of 3), the resulting chronic ReV and ESL are 3.0 ppb (8.7 µg/m^3) and 0.9 ppb (2.6 µg/m^3), respectively.

More directly relevant to the comment, the final chronic ReV for chlorine (Cl_2) of 8.7 µg/m^3 is within a factor of 3 of (i.e., 2.9-fold lower than) the chronic ReV for HCl on a chlorine content basis (i.e., HCl chronic ReV of 26 µg/m^3 × MW of Cl/MW of HCl = 26 µg/m^3 × 35.45/36.46 = 25 µg/m^3 as Cl; TCEQ 2015c). This is a reasonable difference considering, for example, that the original authors of the different studies selected the exposure concentrations that ultimately determined the study PODs (i.e., NOAELs) in both cases.

Comment No. 4:

This review has indicated that TCEQ identified most of the key published human and toxicology studies on Cl_2, and selected the Klonne *et al*. (1987) chronic monkey inhalation exposure study to support the development of long-term values. This peer-reviewed, published study is an understandable choice if human data are not adequate; given the lack of key details from many of the reported human data, coupled with the well-described parameters, chronic exposure scenario, and non-human primate subjects of the Klonne *et al.* (1987) data set, an extrapolation of the results to humans represents a standard approach. Indeed, there are short-term human exposure data that report similar site-of-contact effects as those found in the short-term animal model exposure data, which support that such an extrapolation from non-human primate data to human situations is a reasonable approach.

Nonetheless, an alternative approach for TCEQ to consider might be to use the human volunteer 3-d exposure data published by Schins *et al.* (2000) and relied upon by the European Union (EU) as described in their Risk Assessment Report (RAR) on Chlorine (2007) (extracted from p 74):

> 'Further evidence that 0.5 ppm (1.5 mg/m^3) is a NOAEL in humans is provided by a study of Emmen and Hoogendijk (1997), which was published by Schins et al. (2000). The study was well documented and was done according to Good Clinical Practice. The objectives of this study were:
>
> 1) to determine if chlorine exposure at low levels induces nasal effects in humans as it does in rodents; and
>
> 2) to establish a possible occurrence of respiratory effects in human volunteers exposed to chlorine vapour at concentrations of 0, 0.1, 0.3 and 0.5 ppm (0, 0.3, 0.9 and 1.5 mg/m^3).
>
> The 8 male volunteers were exposed for 6 hours per day on 3 consecutive days to each of the 4 exposure conditions. Data analysis was limited to 7 subjects since one volunteer decided to stop participating for reasons not related to the study.
>
> Some adverse effects were reported by the volunteers and registered by the physician. Most of them were classified as "impossible" or "unlikely" to be treatment related. The following effects were judged as "possible" to be treatment related: sinus tension (1 case), eye irritation (5 cases), coughing (2 cases), nose congestion (2 cases), dry throat (1 case), dry mouth (1 case), throat irritation (1 case), expiratory wheeze (1 case), mucus production in nasal cavity (1 case).
>
> The study concluded that nasal lavage measurements did not support an inflammatory response or irritant effects on the nasal epithelium. Furthermore, no significant effect on lung function parameters was found. The study did not support an inflammatory effect in the nose nor shows changes in the respiratory function at repeated exposure up to 0.5 ppm (1.5 mg/m^3). Also, Shusterman et al. (1998) did not find any significant change in nasal airway resistance in persons exposed to 0.5 ppm (1.5 mg/m^3) for 15 minutes.'

Although 3 days of repeated 6-h exposures do not equal a chronic exposure, and there are no pathology data described in Schins *et al*. (2000) to address very sensitive responses, there are nasal lavage data addressing inflammatory response, a key parameter of irritation effects. They measured interleukin-8 (IL-8), albumin, and inflammatory cell numbers in the nasal lavage fluid, and did not identify any differences compared with the results from exposures to air (the subjects served as their own controls). This dataset, although based on a limited number of subjects, provides a well-conducted study that demonstrated no nasal inflammatory response in human subjects following 3 days of repeated, 6-h exposures to chlorine gas, thus establishing a NOAEL of 0.5 ppm Cl_2. While the EU Scientific Committee on Occupational Exposure Levels

(SCOEL) stated in their 1998 assessment of chlorine that 'Because the effects appear to be related to concentration in the air and not to duration of exposure, there is no requirement for an 8-hour TWA.', and the EU RAR applied the same concept to determine that (excerpted from p 86) '…Human repeated exposure to chlorine is not expected to lead to effects other than irritation observed in the study by Schins *et al*. (2000). We can then take forward to the Risk Characterisation the NOAEL of 0.5 ppm (1.5 mg/m^3) from the human volunteers' study, supported by repeated dose study in monkeys…', actual chronic data in humans to support this position are lacking. Nonetheless, the Schins *et al.* (2000) dataset should be described in the TCEQ DSD for Chlorine, as it is a well-conducted, repeated exposures human volunteer study, which identified a 3-d (6h/day) human NOAEL reported as 0.5 ppm chlorine.

TCEQ Response:

The TCEQ certainly acknowledges the comment that extrapolation from non-human primates is the standard and reasonable approach given the database. As stated in the comment, 3 days of repeated 6-h exposures do not equal a chronic exposure. Thus, this study is judged to be most relevant to the acute assessment, and information on this study as supporting the acute NOAEL of 0.5 ppm (e.g., the lack of nasal inflammatory response) has been added to that section and Table 4.

Minor Comments:

Numerous minor comments were also submitted by Olin™ regarding typos, grammatical errors, missing citations, etc.

TCEQ Response:

The TCEQ appreciates the time and effort put forth to provide these minor comments, which were simply addressed as appropriate through relevant minor revisions.

ACC Comments

Substantive comments relevant to the derivation of toxicity factors are provided and addressed by the TCEQ below.

Comment 1:

<u>TCEQ Uses Effects of Questionable Clinical Relevance to Calculate the Point of Departure</u>

The respiratory system is the primary area of concern for exposure to Cl_2, resulting from the formation of HCl and hydrochlorous acid (HOCl) when in contact with respiratory membranes. Several occupational studies have found the lower respiratory tract to be the primary target of Cl_2 toxicity at higher concentrations, such as those encountered in accidental exposures. There is little information available on the effects of exposure to low concentrations of Cl_2 (<3 parts per million or ppm), however, particularly related to effects in the nasal passages.

While studies have been conducted in rats and mice, data available from studies in non-human primates appear to be the most relevant to human risk assessment. ACC supports TCEQ's

selection of the study of Rhesus monkeys by Klonne et al. (1987) as the basis for the chronic reference value (ReV) and ESL, but disagrees with the conclusion that 0.1 ppm represents a lowest observable adverse effect level (LOAEL) based on the occurrence of nasal lesions. This determination is inconsistent with that of the study authors who indicate that the effects seen at the lower concentrations are of "questionable clinical sigificance." The authors' conclusion suggests that 0.5 ppm should be considered a no observable adverse effect level (NOAEL). This interpretation is consistent with the definition of the NOAEL contained in TCEQ's 2015 guidelines3 and with the conclusions of the European Union.

Klonne et al. (1987) exposed Rhesus monkeys (Macaca mulatta) to concentrations of 0, 0.1, 0.5, and 2.3 ppm Cl2 for 6 hours per day, 5 days per week, for 1 year. Treatment-induced responses were confined to ocular and respiratory tract irritation. Monkeys exposed to the highest chlorine concentration exhibited signs of ocular irritation during the daily exposures and a superficial conjunctival irritation was present in the high exposure group after the 1-year exposure regimen. Histopathological examinations revealed mild treatment-induced lesions in the epithelium of the nose and trachea. These lesions were characterized by mild, focal, epithelial hyperplasia in the absence of epithelial thickening with an associated loss of cilia and goblet cells in the affected areas. Nasal and tracheal lesions were induced by exposure to 2.3 ppm Cl2, while less distinct changes were present in the nasal passages of some animals in the 0.5 and 0.1 ppm groups in the absence of tracheal lesions. There was no evidence of other nasal effects seen in rodents exposed to 2.5 ppm of Cl2 for 2 years, including septal fenestration, increased epithelial mucus, eosinophilic rhinitis, and olfactory sensory cell loss.

The lack of an increase in epithelial mucus in the current study contrasts with the response in monkeys exposed to ambient levels of another irritant gas ozone which resulted in a secretory metaplas a or hyperplasia (Harkema et al 1987).6 Klonne et al. also did not observe evidence of increased intraepithelial mucus in the intrapulmonary airwaves of the monkeys. Such intrapulmonary mucus hypersecretion may have been expected in oronasal breathers like human and non-human primates where the scrubbing action of the nose is reduced and suggests that significant amounts of chlorine did not reach the lower respiratory tract. The authors conclude -

> Given the limited extent of chlorine-induced deciliation in the present study, effects of chlorine exposure on airway clearance mechanisms through inhibition of mucociliary function are probably minimal, especially at the lower chlorine concentrations. Furthermore, exposure of monkeys to [2.3 ppm] produced no pulmonary lesions, indicating that there were no clinically significant effects of this gas on pulmonary defenses.

This conclusion is supported by the observation that the majority of the nasal lesions in the monkeys were found adjacent to the major inspiratory airflow streams in the species (Ibanes et al. 1996).8

The results of this study indicate that 2.3 ppm Cl2 acts as an upper respiratory irritant in monkeys, and suggest a NOAEL of 0.5 ppm based on the minimal nasal mucosal response and the absence of tracheal lesions. The TCEQ's determination that the study supports a LOAEL of 0.1 ppm is not consistent with the location and trace nature of the response at the lower exposure levels and the study authors' conclusion.

TCEQ Response:

The TCEQ has more carefully evaluated results from the key Rhesus monkey study (Klonne et al. 1987) as to adversity and identified a LOEL of 0.5 ppm as the POD. The changes at ≤ 0.5 ppm were very minimal and the biological significance/adversity of these lesions is questionable. For example, while extensive areas of deciliation in the nasal passages of rats impairs mucociliary function in affected regions of the nose, an effect relevant to airway clearance and adversity considerations, mucus may continue to flow over small, limited areas of impaired ciliary function as observed in this study. Consequently, the limited nature of the effects at ≤ 0.5 ppm does not appear to meet the USEPA definition of an adverse effect as "any effect resulting in functional impairment and/or pathological lesions that may affect the performance of the whole organism, or that reduce an organism's ability to respond to an additional challenge" (USEPA 1994). The determination of 0.5 ppm as a LOEL is consistent with the questionable biological significance characterization of effects at ≤ 0.5 ppm by study authors.

Comment 2:

<u>The Proposed Chronic ESL is Inconsistent with the Value Recently Confirmed for Hydrogen Chloride</u>

The proposed chronic ESL for Cl_2 is inconsistent with the considerably higher value of 5.4 ppb (7.9 ug/m^3) originally derived for HCl in 2009 and confirmed as recently as September 2015. Since the mechanism by which Cl_2 forms lesions in the respiratory tract is through the reaction with moisture to form HCl, it is not clear why the value for Cl_2 would be set more than two orders of magnitude lower than for HCl.

Chlorine gas is understood to dissolve in aqueous tissue upon inspiration, resulting in the formation of HCl and HOCl, from which the irritating effects are believed to stem. Comparison of the proposed chronic ESL for Cl_2 with the one set for HCl by TCEQ is an important check of the process that the Council uses to establish ESLs. If TCEQ believes there is a basis for the discrepancy, it should explain why the two values are not inconsistent. In the absence of an appropriate explanation, it would appear that the proposed chronic ESL of 0.04 ppb for Cl_2 is overly conservative.

TCEQ Response:

The TCEQ acknowledges the similarity in MOA for Cl_2 and HCl and the resulting expectation that the respective toxicity factors should perhaps not be multiple orders of magnitude apart. Given the relatively insignificant contribution of H to the molecular weight of HCl, the toxicity factors for both compounds are essentially for chlorine (e.g., µg chlorine/m^3 air), albeit in different

parent chemical forms. The TCEQ has more carefully evaluated results from the key Rhesus monkey study (Klonne et al. 1987) as to adversity and identified a LOEL of 0.5 ppm as the POD. After duration adjustments and with the revised total UF of 30 (UF_H of 10, UF_{Sub} of 3), the resulting chronic ReV and ESL are 3.0 ppb (8.7 $\mu g/m^3$) and 0.9 ppb (2.6 $\mu g/m^3$), respectively.

More directly relevant to the comment, the final chronic ReV for chlorine (Cl_2) of 8.7 $\mu g/m^3$ is within a factor of 3 of (i.e., 2.9-fold lower than) the chronic ReV for HCl on a chlorine content basis (i.e., HCl chronic ReV of 26 $\mu g/m^3$ × MW of Cl/MW of HCl = 26 $\mu g/m^3$ × 35.45/36.46 = 25 $\mu g/m^3$ as Cl; TCEQ 2015c). This is a reasonable difference considering, for example, that the original authors of the different studies selected the exposure concentrations that ultimately determined the study PODs (i.e., NOAELs) in both cases.

Comment 3:

Use of a Default HQ=0.3 as an Additional Level of Conservatism is Unnecessary

CCD recognizes that the TCEQ guidelines call for the use of an HQ of 0.3 to address the potential for cumulative and aggregate exposures from nearby facilities, but finds the use of an additional 3-fold safety factor to be overly conservative in the case of chlorine because of its short atmospheric half-life and the less severe, reversible nature of the toxic lesion found in the key study used by TCEQ. As a reactive chemical, chlorine has a half-life in air of less than 2-4 hours. Any chlorine released from nearby sources will rapidly react, leaving little or no possibility for a cumulative or aggregate effect. Using an higher HQ (e.g., 0.75) is more consistent with the very short atmospheric half-life of chlorine, while still setting the ESL below an HQ of 1.

Use of an HQ=0.3 also is not consistent with the mild and reversible nature of the nasal lesions that TCEQ uses as the basis for the POD. Nasal lesions such as those identified in the chronically exposed monkeys are considered not to be a severe effect and are generally reversible once exposure ceases (Brandenberger et al., 2015).12 Thus, protecting against both a non-severe and a reversible effect offers more flexibility in determination of appropriate conservatism vis-à-vis a target for the HQ.

TCEQ Response:

The TCEQ appreciates these comments by ACC. However, an environmental half-life of several hours (i.e., “atmospheric t½ <2-4 h according to ECHA IUCLID”) is more than enough time for off-site impacts to occur and combine with those from other sources. Even if emissions were from a non-continuous source and the half-life were 1 hour, it would take approximately 5 hours for the resulting chlorine concentration(s) to essentially be eliminated entirely. At 1 hour and average wind speed, the persisting concentrations resulting from emissions could be many miles away, combined with emissions from any other sources impacting the area. Finally, it is noted that there would be no routine chlorine monitoring to confirm the protectiveness of the proposed HQ of 0.75.

Additionally, the TCEQ ReVs and ESLs are appropriately based on mild adverse effects. Severe and/or irreversible effects are not generally used to develop toxicity factors intended to be protective against the most sensitive effects. As such, the TCEQ guidelines intend to apply a factor of 0.3 to ReV values based on mild effects, as is the case with chlorine. Finally, it is simply noted that reversibility arguments are not relevant to chronic ReVs (or the HQ factor applied to them) since they are derived to be protective of *continuous* lifetime exposure (i.e., without the opportunity for reversibility due to the lack of exposure).

In summary, the TCEQ does not find the short half-life in air or mild adverse effect arguments for a higher HQ compelling and a factor of 0.3 continues to be applied to the chronic ReV in the final DSD.

Comment 4:

Derivation of an Alternative Chronic ESL

Applying the same benchmark dose (BMD)approach to the data from Klonne *et al.* - based on the occurrence of distinct nasal and tracheal lesions at 2.3 ppm - produces a POD of 0.47 ppm for the $BDML_{10}$ and a chronic ReV of 2.8 ppb. This value is more in line with the chronic ESL established for HCl, but requires the use of HQ=1.0. Further adjusting for a HQ = 0.3, per TCEQ guidelines, results in a chronic ESL of 0.83 ppb. Although still significantly lower than the HCl value, this alternative value is more in line with the nature of the effects seen in the key study.

TCEQ Response:

The TCEQ has more carefully evaluated results from the key Rhesus monkey study (Klonne et al. 1987) as to adversity and identified a LOEL of 0.5 ppm as the POD. After duration adjustments and with the revised total UF of 30 (UF_H of 10, UF_{Sub} of 3), the resulting chronic ReV and ESL are 3.0 ppb (8.7 µg/m^3) and 0.9 ppb (2.6 µg/m^3), respectively. The final chronic ReV for chlorine (Cl_2) of 8.7 µg/m^3 is within a factor of 3 of (i.e., 2.9-fold lower than) the chronic ReV for HCl on a chlorine content basis (i.e., HCl chronic ReV of 26 µg/m^3 × MW of Cl/MW of HCl = 26 µg/m^3 × 35.45/36.46 = 25 µg/m^3 as Cl; TCEQ 2015c). This is a reasonable difference considering, for example, that the original authors of the different studies selected the exposure concentrations that ultimately determined the study PODs (i.e., NOAELs) in both cases.

Olin™
CHLOR ALKALI
PRODUCTS AND VINYLS

Blue Cube Operations LLC

1821 Larkin Center Drive
Midland, MI 48674
www.OlinChloralkali.com

VIA ELECTRONIC MAIL - tox@tceq.texas.gov

October 20, 2016

Toxicology Division, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Re: Development Support Document – Chlorine (CAS Registry Number 7782-50-5), Proposed June 2016

Dear Sir, Madame,

As a major chlorine producer and user in Texas, Olin Corporation is pleased to have the opportunity to review and provide comments on the on the Effects Screening Levels (ESLs) for chlorine proposed by the Texas Commission on Environmental Quality (TCEQ). These comments will focus on aspects of the proposed $^{chronic}ESL_{threshold(nc)}$, as that is the key value for Olin Corporation. Olin is concerned with TCEQ's proposal to significantly reduce the chronic ESL value from 1.45 micrograms per cubic meter (µg/m^3), equal to 0.52 parts per billion (ppb), to a value of 0.10 µg/m^3 (0.04 ppb). The proposed 13-fold reduction in the chronic ESL will require chlor-alkali manufacturing and other facilities in the state to conduct complicated modeling to estimate fugitive emissions with little or no public health benefit.

TCEQ has identified a rich database of relevant studies to inform the determination of Effects Screening Levels (ESL) values for chlorine. However, it seems that certain aspects have not received the attention they merit. As a reactive chemical, chlorine (Cl_2) has a very short half-life in air (atmospheric t½ <2-4 h according to ECHA IUCLID[1]). Thus any chlorine present from other sources will also be very short-lived, leaving little or no possibility for a cumulative or aggregate effect. Chlorine gas is understood to dissolve in aqueous tissue upon inhalation, resulting in the formation of HCl and HOCl, from which the irritating effects are believed to stem. Thus comparison of the proposed $^{chronic}ESL_{threshold(nc)}$ for Cl_2 with the one set for HCl by TCEQ (2015) is important since the effects driving both these $^{chronic}ESL_{threshold(nc)}$ values are nasal/upper respiratory irritation. The 2015 $^{chronic}ESL_{threshold(nc)}$ value for HCl is 5.4 ppb, which is 135-fold higher than the $^{chronic}ESL_{threshold(nc)}$ currently proposed for Cl_2, despite the fact that both are based on nasal/upper respiratory irritation, in the case of Cl_2 apparently caused by HCl + HOCl derived from Cl_2. It is not clear why there should be such a large discrepancy between these two values, although it is perhaps reasonable to consider a factor of two reduction in comparing the HCl value for Cl_2 due to the presence of two chlorine atoms in Cl_2 and thus twice the capacity for formation of HCl and perhaps twice the subsequent irritation on a molar basis. Thus one might expect a value in the range of 2.7 ppb for the Cl_2 $^{chronic}ESL_{threshold(nc)}$, using that simple comparative approach. Indeed, another comparison with a well-recognized nasal/upper respiratory irritant includes formaldehyde, where TCEQ set a $^{chronic}ESL_{threshold(nc)}$ value of 2.7 ppb (2014). Again, the $^{chronic}ESL_{threshold(nc)}$ value determined for formaldehyde, certainly a potent nasal/upper respiratory irritant, is significantly higher (67.5-fold

[1] 'In the atmosphere, Cl_2 will degrade during daylight, with half-lives ranging from minutes to several hours, depending on latitude, season, and time of day'; ECHA Chemical Safety Report for Chlorine, 2015.

higher) than the $^{chronic}ESL_{threshold(nc)}$ value proposed for Cl_2. It would be helpful to understand the rationale for these significant differences, given the similarity in chemical composition for Cl_2 vs HCl, and the likely similarity in irritant potency effects for Cl_2 vs formaldehyde. Alternatively, it would appear that the proposed $^{chronic}ESL_{threshold(nc)}$ value for Cl_2 is overly conservative at the proposed 0.04 ppb.

This review has indicated that TCEQ identified most of the key published human and toxicology studies on Cl_2, and selected the Klonne *et al*. (1987) chronic monkey inhalation exposure study to support the development of long-term values. This peer-reviewed, published study is an understandable choice if human data are not adequate; given the lack of key details from many of the reported human data, coupled with the well-described parameters, chronic exposure scenario, and non-human primate subjects of the Klonne *et al.* (1987) data set, an extrapolation of the results to humans represents a standard approach. Indeed, there are short-term human exposure data that report similar site-of-contact effects as those found in the short-term animal model exposure data, which support that such an extrapolation from non-human primate data to human situations is a reasonable approach.

Nonetheless, an alternative approach for TCEQ to consider might be to use the human volunteer 3-d exposure data published by Schins *et al.* (2000) and relied upon by the European Union (EU) as described in their Risk Assessment Report (RAR) on Chlorine (2007) (extracted from p 74):

> 'Further evidence that 0.5 ppm (1.5 mg/m^3) is a NOAEL in humans is provided by a study of Emmen and Hoogendijk (1997), which was published by Schins et al. (2000). The study was well documented and was done according to Good Clinical Practice. The objectives of this study were:
> 1) to determine if chlorine exposure at low levels induces nasal effects in humans as it does in rodents; and
> 2) to establish a possible occurrence of respiratory effects in human volunteers exposed to chlorine vapour at concentrations of 0, 0.1, 0.3 and 0.5 ppm (0, 0.3, 0.9 and 1.5 mg/m^3).
> The 8 male volunteers were exposed for 6 hours per day on 3 consecutive days to each of the 4 exposure conditions. Data analysis was limited to 7 subjects since one volunteer decided to stop participating for reasons not related to the study. Some adverse effects were reported by the volunteers and registered by the physician. Most of them were classified as "impossible" or "unlikely" to be treatment related. The following effects were judged as "possible" to be treatment related: sinus tension (1 case), eye irritation (5 cases), coughing (2 cases), nose congestion (2 cases), dry throat (1 case), dry mouth (1 case), throat irritation (1 case), expiratory wheeze (1 case), mucus production in nasal cavity (1 case).
> The study concluded that nasal lavage measurements did not support an inflammatory response or irritant effects on the nasal epithelium. Furthermore, no significant effect on lung function parameters was found. The study did not support an inflammatory effect in the nose nor shows changes in the respiratory function at repeated exposure up to 0.5 ppm (1.5 mg/m3). Also, Shusterman et al. (1998) did not find any significant change in nasal airway resistance in persons exposed to 0.5 ppm (1.5 mg/m3) for 15 minutes.'

Although 3 days of repeated 6-h exposures do not equal a chronic exposure, and there are no pathology data described in Schins *et al*. (2000) to address very sensitive responses, there are nasal lavage data addressing inflammatory response, a key parameter of irritation effects. They measured interleukin-8 (IL-8), albumin, and inflammatory cell numbers in the nasal lavage fluid, and did not identify any differences compared with the results from exposures to air (the subjects served as their own controls). This dataset, although based on a limited number of subjects, provides a well-conducted study that demonstrated no nasal inflammatory response in human subjects following 3 days of repeated, 6-h exposures to Chlorine gas, thus establishing a NOAEL of 0.5 ppm Cl_2. While the EU Scientific Committee on Occupational Exposure Levels (SCOEL) stated in their 1998 assessment of chlorine that 'Because the effects appear to be related to concentration in the air and not to duration of exposure, there is no requirement for an 8-hour TWA.', and the EU RAR applied the same concept to determine that (excerpted from p 86) '…Human repeated exposure to chlorine is not expected to lead to effects other than irritation observed in the study by Schins *et al*. (2000). We can then take forward to the Risk Characterisation the NOAEL of 0.5 ppm (1.5 mg/m^3) from the human volunteers' study, supported by

repeated dose study in monkeys…', actual chronic data in humans to support this position are lacking. Nonetheless, the Schins *et al.* (2000) dataset should be described in the TCEQ DSD for Chlorine, as it is a well-conducted, repeated exposures human volunteer study, which identified a 3-d (6h/day) human NOAEL reported as 0.5 ppm chlorine.

This review has indicated that TCEQ applied their own DSD guidance as described in their guidance document (2006, 2015) in developing the $^{chronic}ESL_{threshold(nc)}$, with conduct of Benchmark Dose (BMD) modelling of the dose-response for the critical endpoint (nasal/upper respiratory epithelial remodelling effects from chlorine), to select a point-of-departure (POD) based on the $BMDL_{10}$, and adjustment of that $BMDL_{10}$ value to account for frequency and duration of exposure to address a 24-h daily exposure, followed by application of selected uncertainty factors for a non-cancer effect. However, a simple application of guidance is not always the only suitable method to determine appropriate risk values. In light of the comparative values for Cl_2 vs HCl, alternative approaches to determining a risk value should be considered.

Indeed, the currently proposed $^{chronic}ESL_{threshold(nc)}$ of 0.04 ppb is considerably lower than the previous value, which was 1.5 $\mu g/m^3$, or 0.5 ppb, set in 2003, and 135-fold lower than the TCEQ (2015) $^{chronic}ESL_{threshold(nc)}$ value for HCl.

Olin recommends that TCEQ consult with Ms. Annie Jarabek, USEPA NCEA, a recognized expert in toxicity of inhaled chlorine, who has conducted research on this topic. She has unpublished data that may provide additional information useful to the determination of a $^{chronic}ESL_{threshold(nc)}$ value and other values for Chlorine.

In reviewing the draft DSD for chlorine, several opportunities for additional alternative, potentially improved, approaches were identified; these are described below for consideration by TCEQ.

1) Apply a hazard quotient (HQ) of 0.75 instead of 0.3, given the short atmospheric half-life of chlorine and the low severity and reversibility of the site-of-contact irritation effects on nasal mucosa.
Based on the TCEQ guidance[2] (2006, 2015), the application of an HQ of 0.3 allows for the potential existence of several sources of the chemical under consideration ('cumulative and aggregate exposure'), with an expectation that total air values would not exceed an overall HQ of 1. This approach is a conservative one that supports the guidance's goal of 'no significant risk'. However, such an additional 3-fold extra conservatism is not needed in the case of chlorine for several reasons, including its atmospheric reactivity and resultant short half-life and the less severe, reversible nature of the toxic lesion.

[2] '**1.4 Specific Risk Management Objectives (No Significant Risk Levels)**
In order to ensure consistent protection of human health, chemical-specific ESLs are based on a defined risk management objective of no significant risk. The no significant risk level for an individual chemical is defined as the concentration associated with a hazard quotient (HQ) of 1 and the concentration associated with a theoretical excess lifetime cancer risk of one in 100,000 (1×10^{-5}). …

In consideration of cumulative and aggregate exposure, the Toxicology Section (TS) uses an HQ of 0.3 to calculate short-term and long-term ESLs for chemicals with a nonlinear dose-response assessment. … ESLs developed in accordance with these no significant risk levels are intended to prevent adverse effects potentially associated with cumulative and aggregate exposures as defined in Section 1.2.'; excerpted from p 3, TCEQ, 2006, Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors.

a) As stated above, the reactive chemical chlorine has a very short half-life in air (atmospheric t½ <2-4 h according to ECHA IUCLID[3]). Thus any chlorine present from other sources will also be very short-lived, leaving little or no possibility for a cumulative or aggregate effect to necessitate the additional 3-fold safety factor. Using an HQ of 0.75 would be supported by the very short atmospheric half-life of chlorine and meets the guidance goals of an overall HQ <1.
b) The critical effect identified for long-term exposure to chlorine gas is nasal lesions, identified as the 'combined incidences of hyperplasia in the nasal epithelium with loss of goblet cells and cilia,' (TCEQ, 2016) in male and female monkeys following 1 year of inhalation exposure to chlorine. The incidence of these nasal lesions was 'mild concentration-related respiratory epithelial hyperplasia with focal loss of cilia over the range of concentrations tested (0, 0.1, 0.5, and 2.3 ppm)'. Nasal lesions such as those identified in the chronically exposed monkeys are considered not to be a severe effect; indeed they were defined as 'mild'; in addition, typically such nasal lesions are reversible once exposure ceases (see Brandenberger *et al.,* 2015). Thus, protecting against both a non-severe and a reversible effect offers more flexibility in the determination of appropriate conservatism *vis-à-vis* a target for HQ.

If TCEQ were to adopt this recommendation, and apply an HQ of 0.75, for example, the $^{chronic}ESL_{threshold(nc)}$ would increase from 0.04 ppb to 0.09 ppb (0.12 ppb x 0.75 = 0.09 ppb), still over 40-fold below the chronic POD_{adj} identified of 3.7 ppb based on Benchmark Dose Low (BMDL) modelling of the Klonne *et al.* (1987) chronic inhalation monkey nasal lesion data.

2) Apply selected Uncertainty Factors (UF) to the POD_{adj} based on available information:
Given the reliance on monkey data to determine the $^{chronic}ESL_{threshold(nc)}$ for chlorine, and both the physiological similarity in nasal passages between humans and non-human primates and the expectation that a reactive chemical like chlorine will exert its toxic effects *via* the same mode-of-action for a site-of-contact effect in monkeys as in humans, TCEQ should consider reducing the UF used to account for potential species differences in toxicodynamics from three (3) to one (1), similar to the UF applied for differences in toxicokinetics[4]. This would result in a total UF of 10 to address 'human variability and sensitive subpopulations (*i.e*., children, the elderly, individuals with pre-existing conditions).'

If TCEQ were to adopt this recommendation, and apply the UF of 1 for toxicodynamics instead of the UF of 3, the final $^{chronic}ESL_{threshold(nc)}$ value would increase from 0.04 ppb to 0.11 ppb (chronic ReV= 0.37 ppb; 0.37 ppb x HQ 0.3 = 0.11), still over 33-fold below the chronic POD_{adj} identified of 3.7 ppb based on Benchmark Dose Low (BMDL) modelling of the Klonne *et al.* (1987) chronic inhalation monkey nasal lesion data.

[3] 'In the atmosphere, Cl_2 will degrade during daylight, with half-lives ranging from minutes to several hours, depending on latitude, season, and time of day'; ECHA Chemical Safety Report for Chlorine, 2015.

[4] 'The subchronic-to-chronic UF (UFsub) was not applicable since a chronic duration study was used.

- UFH of 10 was applied to account for human variability and sensitive subpopulations (*i.e*., children, the elderly, individuals with pre-existing conditions) to the effects of chlorine.
- UFA of 3 for animal-to-human variability was used because a dosimetric adjustment was made to account for toxicokinetic differences but not toxicodynamic differences.
- UFL of 1 was used because BMD modeling was conducted and the resulting POD (BMCL10) is considered a NOAEL.
- UFD of 1 was used because the database for chlorine was considered complete and of high quality.

A total UF of 30 was applied to the PODHEC of 3.678 ppb to derive the chronic ReV of 0.12 ppb (rounded to two significant figures)'. Excerpted from p 22, TCEQ, 2016, Draft DSD for Chlorine.

If TCEQ were to apply both these alternative approaches to determination of the $^{chronic}ESL_{threshold(nc)}$ for chlorine, the composite UF would be 10 instead of 30, with an HQ of 0.75, and the $^{chronic}ESL_{threshold(nc)}$ would be 0.28 ppb instead of 0.04 ppb, still >13-fold below the chronic POD_{adj} identified as 3.7 ppb based on Benchmark Dose Low 10% response ($BMDL_{10}$) modelling of the Klonne *et al.* (1987) chronic inhalation monkey nasal lesion data. This potential $^{chronic}ESL_{threshold(nc)}$ value would also still fall considerably below the current 5.4 ppb $^{chronic}ESL_{threshold(nc)}$ value TCEQ determined for HCl, although the irritation effect for Cl_2 stems from its dissolution in tissue aqueous to HCl + HOCl.

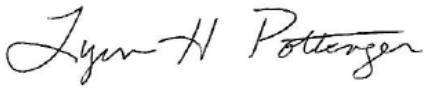
Given that current understanding of toxicology would predict a similar MOA across these closely related species—non-human primates and humans—for a site-of-contact effect from a reactive chemical such as chlorine, the proposed total of >13-fold below the POD_{adj}, with its implicit conservatisms from the selection of the $BMDL_{10}$ value as the POD and a mild, reversible effect (nasal epithelial lesions in monkeys following chronic inhalation exposure), is considered adequate protection, especially when compared with the current TCEQ (2015) $^{chronic}ESL_{threshold(nc)}$ value for HCl.

NB: All the alternative approaches described above result in $^{chronic}ESL_{threshold(nc)}$ values that are still below the previously determined $^{chronic}ESL_{threshold(nc)}$ of 0.5 ppb from 2003.

Finally, additional comments and suggested revisions, including relatively minor errors, either missing information (reference citations) or incorrect information (error in Table 4), additional considerations, and minor typo-type/grammatical errors, were noted and are all described in Appendix 1 for your convenience.

We would be pleased to discuss the above comments and any questions you might have on the concepts and recommendations presented above.

Respectfully submitted,



Lynn H. Pottenger, Ph.D., DABT

Toxicology Consultant Leader

Olin

Blue Cube Operations, LLC

tel: +1-989-638-7036
email: lpottenger@olinbc.com

References:

Amoore, J.E., and Hautala, E. 1983. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol. 3(6):272-290.

Arts, J.H.E., Rennen, M.A.J., de Heer, C. (2006). Inhaled formaldehyde: Evaluation of sensory irritation in relation to carcinogenicity. Regulatory Toxicology and Pharmacology 44: 144–160.

Brandenberger, C., J.A. Hotchkiss, S.M. Krieger, L.H. Pottenger, J.R. Harkema. (2015). Inhalation exposure to ethylene induces eosinophilic rhinitis and nasal epithelial remodeling in Fischer 344 rats. Chemico-Biological Interactions, 241: 66-75.

ECHA Chemical Safety Report for Chlorine, 2015.

EU RAR on Chlorine. 2007.

Ibanes, J.D., Leininger, J.R., Jarabek, A.M., Harkema, J.R., Hotchkiss, J.A., and Morgan, K.T. 1996. Reexamination of Respiratory Tract Responses in Rats, Mice, and Rhesus Monkeys Chronically Exposed to Inhaled Chlorine. Inhalation Toxicology: 8:9: 859-876.

Schins, RPF, Emmen, H, Hoogendijk, L, and Borm, PJA. 2000. Nasal inflammatory and respiratory parameters in human volunteers during and after repeated exposure to chlorine. Eur. Respir. J. 16: 626-632.

SCOEL. 1998. Summary on Chlorine OEL.

TCEQ. 2016. Draft DSD for Chlorine.

TCEQ. 2014. Final DSD for Formaldehyde.

TCEQ. 2015. Final DSD for HCl.

TCEQ. 2006. Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors.

TCEQ. 2015. Guidelines to Develop Toxicity Factors.

Appendix 1

Suggested Revisions/Additions/Corrections:
P3, Table 3: Consider including the odor threshold for chlorine in this table of phys-chem parameters. Amoore and Hautala (1983) reported an odor threshold of 0.31 ppm for chlorine, with a range from 0.02 to 0.8 ppm reported by the EU Risk Assessment Report on Chlorine (2007) (Table 4-16).

P4, line 31: The statement about the effects on the trigeminal nerve should be referenced.

P 9, Table 4: the reference to a 2-h exposure to 2 ppm cited for Joosting & Verbeck (1974) should be corrected to identify this exposure as a LOAEL.

P 9: While Table 4 offers a very useful overview of the acute human data for chlorine effects, there are several improvements that would increase its utility. For example, it should clarify the selected POD as 0.5 ppm for 1-h based on Anglen (1981) (currently shows duration as 15 min-4h); it should include as a separate entry the Rotman *et al.* (1983) NOAEL as 0.5 ppm, 4 h; it is missing an entry from the reference Joosting and Verbeck (1974) (see below); and it should include data from the Schins *et al.* (2000) reference (see below).

Consider including an additional line referring to the results from the 2-h exposure to 1 ppm chlorine reported by Joosting and Verbeck (1974), which identified the NOAEL: 'At 0.5 and 1 ppm all the group means were below the level of just perceptible (code 1), and the individual means figured below distinctly perceptible (code 2)…', which might read as follows, with a similar suggested entry for the Schins *et al.* (2000) data:

Concentration (ppm)	Exposure Time	Effect	Study
1.0 (NOAEL)	2 h	Mean irritation of eyes, nose, and throat in healthy subjects below the level of 'just perceptible; no changes in pulmonary function	Joosting & Verberk, 1974
0.5 (NOAEL)	6 h/3 days	No adverse effects of chlorine exposure to nasal and respiratory parameters were found at repeated exposure of human volunteers to chlorine (6 h, 3 days) up to 0.5 ppm.	Schins *et al*., 2000

P11, line 8: Arts *et al*., 2006, while cited on page 1 of the draft DSD on Chlorine, is not included in the reference list. Recommend the full reference be added to the reference list as follows:

> Arts, J.H.E., Rennen, M.A.J., de Heer, C. (2006). Inhaled formaldehyde: Evaluation of sensory irritation in relation to carcinogenicity. Regulatory Toxicology and Pharmacology 44: 144–160.

P12, lines 20/21: Given the large number of datasets that demonstrate similar effects at similar levels of chlorine exposure, the confidence in the database as discussed under UF_D should be high (and NOT medium to high).

P13, Table 5: same as above, consider the database of high quality

P16, line 25: statement about the TWA is not clear: 'Time-weighted averages (TWAs) 25 were <0.1 ppm, with the highest of <0.1- 0.3 ppm' Please clarify.

P16, line 30: Recommend inserting 'chronic' and 'repeated' to read: '…health impairment is associated with chronic and repeated exposure to chlorine and/or chlorine dioxide.'

PP18/19, section 4.1.1.2.1: it would help clarify the overall description of the Klonne *et al.* (1987) results to include the following: a clear statement that histopathological evaluation was conducted on the lungs and that no effects were identified following chronic (1-yr) exposure to chlorine; and discussion of the dual infestation of the majority of monkeys with nematodes (nasal; 27 animals/32 total) and mites (pulmonary; 28 animals/32 total), and TCEQ's perspective on potential impact of these infestations on the results. One possibility is that the infestation rendered the monkeys more sensitive to any nasal effects, and thus perhaps they should be considered as representing a sensitive subgroup.

PP 18/19/20: Consider including more information from re-analyses of Klonne *et al*. (1987) and Wolf *et al*. (1995), published by Ibanes *et al.* (1996) in the sections describing these studies. For example, Ibanes *et al.* (1996) identified the presence of eosinophils in rats exposed to chlorine chronically from re-analysis/re-staining of the slides from Wolf *et al.* (1995); no such infiltration of eosinophils was found in re-analysis of slides from the Klonne *et al.* monkey study, which underlines a species difference between rodent and monkey in any inflammatory response to chronic chlorine exposure. Also, there was no quantitative increase in intraepithelial mucosubstances identified in the exposed monkeys by Ibanes *et al.* (1996), although this was a key response in rodents. The Ibanes *et al.* (1996) publication discussed that in the non-human primates, the only response was mild epithelial hyperplasia with focal deciliation, very different from the more robust rodent response, raising the question about which species was more appropriate as a model for potential human targets. A more thorough discussion of these key differences would better inform the decision on how to use the non-human primate data.

P19, lines 11-15 and p 20, line 34: TCEQ combined the incidences of male and female nasal epithelial hyperplasia, both trace and mild. Klonne *et al.* (1987) did not provide statistical analyses on these data, nor recommend the incidences be combined. Given the question of biological significance of a 'trace' effect, and that there was one control/unexposed monkey identified with this effect, it may make sense to consider statistical analysis of the nasal epithelial hyperplasia data. It is likely that 0.1 ppm should be considered the NOAEL, as opposed to a LOAEL, which is the current TCEQ position.

P20; line 1: Ibanes *et al.* (1996) is not listed in the references, so should be added to the references:

Ibanes, J.D., Leininger, J.R., Jarabek, A.M., Harkema, J.R., Hotchkiss, J.A., and Morgan, K.T. 1996. Reexamination of Respiratory Tract Responses in Rats, Mice, and Rhesus Monkeys Chronically Exposed to Inhaled Chlorine. Inhalation Toxicology: 8:9: 859-876.

P22; lines 26/27: UF_H: Consider the possibility that the concurrent dual infestations increased the sensitivity of the monkeys to nasal irritant effects, and whether this consideration, combined with the use of non-human primate data, should drive a lower UF_H, perhaps 3-5 instead of 10.

P22; lines 29/30: UF_A: Given that the MOA/Toxicodynamics is considered to be the same for humans as for non-human primates, primarily driven by formation of HCl +HOCl and its subsequent irritation capability, consider whether UF_A should be equivalent to 1 or 2, rather than 3.

PP22/23; lines 35/36 and 1-5: If the above-proposed revisions to UF_H and/or UF_A are accepted, then this paragraph will need to be revised.

P23; lines 7-10: Given the fact that the critical effect is mild, not life-threatening, and reversible, consider whether an HQ of 0.75 is appropriate to determine the $^{chronic}ESL_{threshold(nc)}$.

P24: Table 7: If the above recommendations are accepted, then this table would need to be revised.

P25; Table 8: Consider including the values developed by TCEQ for HCl in this table as they are relevant to the discussion, given the similar MOAs for Cl_2 and HCl critical effects.

P26; line 3: Correct the incorrect value for the POD_{HEC} that is listed currently (3.57 ppb) to read: 3.68 ppb

P26; line 11: Correct the current verbiage ('…inhalation observed adverse effect level….') by revising to read: '…inhalation no adverse effect level…', as the POD_{HEC} based on a BMDL is by definition a surrogate for a NOAEL value.

P26; line 11: Correct the incorrect value for the POD_{HEC} that is listed currently (3.57 ppb) to read: 3.68 ppb.

Typographical errors:

P iii: definitions of several different ESL values are missing the hyphen for 'dose-response', which is included in later uses of the term 'dose-response', so should be added to these definitions for consistency.

P v: last line; World Health Organization should be capitalized

P 16, line 24: delete extra 'during'

P 18, line 3: delete extra space after '8-' and before 'h'

P 18, line 6: delete extraneous 't' on 'not' to read: '…but no dose-response relationship…'

P 18, line 7: insert missing hyphen to read: 'No dose-response relationship…'

P 18, line 21: assume mis-spelling with missing 'o': please check 'posteranterior'

P 27, line 27: insert missing Ibanes *et al*. (1996) reference

P 29, lines 8/9: insert missing Arts *et al.* (2006) reference

P 32 (Appendix A), line 15: Substitute correct table number for current 'Table +'

BY ELECTRONIC MAIL

October 20, 2016

Toxicology Division, MC 168
Texas Commission on Environmental Quality
P.O. Box 13087
Austin, TX 78711-3087

Re: Development Support Document – Chlorine (CAS Registry Number 7782-50-5), Proposed June 2016

To Whom It May Concern:

The Chlorine Chemistry Division[1] (CCD) of the American Chemistry Council appreciates the opportunity to provide comments on the Effects Screening Levels (ESLs) for chlorine (Cl_2) proposed by the Texas Commission on Environmental Quality (TCEQ). ACC is concerned about TCEQ's proposal to significantly reduce the chronic ESL from 1.45 micrograms per cubic meter ($\mu g/m^3$), equal to 0.5 parts per billion (ppb), to 0.10 $\mu g/m^3$ (0.04 ppb). The proposed reduction in the chronic ESL will require chlor-alkali manufacturing and other facilities in the state to conduct complicated modeling to estimate fugitive emissions - with little or no public health benefit. Our comment focuses on the following issues:

- Consideration of health effects of questionable clinical significance in the determination of the point of departure (POD) for the key study;
- Inconsistency of the proposal with the chronic ESL recently established for hydrogen chloride (HCl); and
- Use of the default threshold of a hazard quotient (HQ) of 0.3 to calculate the chronic ESL despite chlorine's very short atmospheric half-life and the mild and reversible nature of the observed effects.

TCEQ Uses Effects of Questionable Clinical Relevance to Calculate the Point of Departure

The respiratory system is the primary area of concern for exposure to Cl_2, resulting from the formation of HCl and hydrochlorous acid (HOCl) when in contact with respiratory membranes. Several occupational studies have found the lower respiratory tract to be the primary target of Cl_2 toxicity at higher concentrations, such as those encountered in accidental exposures. There is little information available on the effects of exposure to low concentrations of Cl_2 (<3 parts per million or ppm), however, particularly related to effects in the nasal passages.

[1] The Chlorine Chemistry Division of the American Chemistry Council represents major producers and users of chlorine in North America. The Division works to promote and protect the sustainability of chlorine chemistry processes, products and applications in accordance with the principles of Responsible Care®.

While studies have been conducted in rats and mice, data available from studies in non-human primates appear to be the most relevant to human risk assessment. ACC supports TCEQ's selection of the study of Rhesus monkeys by Klonne *et al.* (1987)[2] as the basis for the chronic reference value (ReV) and ESL, but disagrees with the conclusion that 0.1 ppm represents a lowest observable adverse effect level (LOAEL) based on the occurrence of nasal lesions. This determination is inconsistent with that of the study authors who indicate that the effects seen at the lower concentrations are of "questionable clinical significance." The authors' conclusion suggests that 0.5 ppm should be considered a no observable adverse effect level (NOAEL). This interpretation is consistent with the definition of the NOAEL contained in TCEQ's 2015 guidelines[3] and with the conclusions of the European Union.[4]

Klonne *et al.* (1987) exposed Rhesus monkeys (*Macaca mulatta*) to concentrations of 0, 0.1, 0.5, and 2.3 ppm Cl_2[5] for 6 hours per day, 5 days per week, for 1 year. Treatment-induced responses were confined to ocular and respiratory tract irritation. Monkeys exposed to the highest chlorine concentration exhibited signs of ocular irritation during the daily exposures and a superficial conjunctival irritation was present in the high exposure group after the 1-year exposure regimen. Histopathological examinations revealed mild treatment-induced lesions in the epithelium of the nose and trachea. These lesions were characterized by mild, focal, epithelial hyperplasia in the absence of epithelial thickening with an associated loss of cilia and goblet cells in the affected areas. Nasal and tracheal lesions were induced by exposure to 2.3 ppm Cl_2, while less distinct changes were present in the nasal passages of some animals in the 0.5 and 0.1 ppm groups in the absence of tracheal lesions. There was no evidence of other nasal effects seen in rodents exposed to 2.5 ppm of Cl_2 for 2 years, including septal fenestration, increased epithelial mucus, eosinophilic rhinitis, and olfactory sensory cell loss.

The lack of an increase in epithelial mucus in the current study contrasts with the response in monkeys exposed to ambient levels of another irritant gas ozone which resulted in a secretory metaplasia or hyperplasia (Harkema et al 1987).[6] Klonne *et al.* also did not observe evidence of increased intraepithelial mucus in the intrapulmonary airwaves of the monkeys. Such intrapulmonary mucus hypersecretion may have been expected in oronasal breathers like human and non-human primates where the scrubbing action of the nose is reduced and suggests that significant amounts of chlorine did not reach the lower respiratory tract. The authors conclude -

> Given the limited extent of chlorine-induced deciliation in the present study, effects of chlorine exposure on airway clearance mechanisms through inhibition of mucociliary

---

2 Klonne DR *et al.* One-year inhalation toxicity study of chlorine in rhesus monkeys (*Macaca mulatta*). *Fund Appl Toxicol* 9(3):557-572 (1987).

3 TCEQ. TCEQ Guidelines to Develop Toxicity Factors. RG442 (September 2015), at 56. The TCEQ definition for NOAEL indicates that "effects may be produced at [the NOAEL], but they are not considered adverse or precursors of adverse effects."

4 European Union. Risk Assessment Report – Chlorine. Risk Assessment (Human Health). (December 2007). Available at https://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation. (EU RAR)

5 Equivalent to 0.3, 1.5, and 6.7 milligrams per cubic meter (mg/m^3).

6 Harkema JR *et al.* Effects of an ambient level of ozone on primate nasal epithelial mucosubstances: quantitative histochemistry. *Am J Pathol* 127(1):90-96 (1987).

> function are probably minimal, especially at the lower chlorine concentrations. Furthermore, exposure of monkeys to [2.3 ppm] produced no pulmonary lesions, indicating that there were no clinically significant effects of this gas on pulmonary defenses.[7]

This conclusion is supported by the observation that the majority of the nasal lesions in the monkeys were found adjacent to the major inspiratory airflow streams in the species (Ibanes *et al.* 1996).[8]

The results of this study indicate that 2.3 ppm Cl_2 acts as an upper respiratory irritant in monkeys, and suggest a NOAEL of 0.5 ppm based on the minimal nasal mucosal response and the absence of tracheal lesions. The TCEQ's determination that the study supports a LOAEL of 0.1 ppm is not consistent with the location and trace nature of the response at the lower exposure levels and the study authors' conclusion.

The Proposed Chronic ESL is Inconsistent with the Value Recently Confirmed for Hydrogen Chloride

The proposed chronic ESL for Cl_2 is inconsistent with the considerably higher value of 5.4 ppb (7.9 ug/m^3) originally derived for HCl in 2009 and confirmed as recently as September 2015.[9] Since the mechanism by which Cl_2 forms lesions in the respiratory tract is through the reaction with moisture to form HCl, it is not clear why the value for Cl_2 would be set more than two orders of magnitude lower than for HCl.

Chlorine gas is understood to dissolve in aqueous tissue upon inspiration, resulting in the formation of HCl and HOCl, from which the irritating effects are believed to stem. Comparison of the proposed chronic ESL for Cl_2 with the one set for HCl by TCEQ is an important check of the process that the Council uses to establish ESLs. If TCEQ believes there is a basis for the discrepancy, it should explain why the two values are not inconsistent.[10] In the absence of an appropriate explanation, it would appear that the proposed chronic ESL of 0.04 ppb for Cl_2 is overly conservative.

Use of a Default HQ=0.3 as an Additional Level of Conservatism is Unnecessary

CCD recognizes that the TCEQ guidelines call for the use of an HQ of 0.3 to address the potential for cumulative and aggregate exposures from nearby facilities, but finds the use of an additional 3-fold safety factor to be overly conservative in the case of chlorine because of its short atmospheric half-life and the less severe, reversible nature of the toxic lesion found in the key study used by TCEQ. As a reactive chemical, chlorine has a half-life in air of less than 2-4 hours.[11] Any chlorine released from

---

7 Klonne DR *et al.*, at 570.

8 Ibanes JD *et al.* Reexamination of respiratory tract responses in rats, mice, and Rhesus monkeys chronically exposed to inhaled chlorine. *Inhal Toxicol* 8:859-876 (1996).

9 TCEQ. Development Support Document for Hydrogen Chloride (CAS Registry Number 7647-01-0). Revised September 14, 2015.

10 The presence of two chlorine atoms in Cl_2, compared to one in HCl, may provide a partial explanation for the difference, but cannot explain a difference of more than two orders of magnitude.

11 EU RAR, at 37.

nearby sources will rapidly react, leaving little or no possibility for a cumulative or aggregate effect. Using an higher HQ (e.g., 0.75) is more consistent with the very short atmospheric half-life of chlorine, while still setting the ESL below an HQ of 1.

Use of an HQ=0.3 also is not consistent with the mild and reversible nature of the nasal lesions that TCEQ uses as the basis for the POD. Nasal lesions such as those identified in the chronically exposed monkeys are considered not to be a severe effect and are generally reversible once exposure ceases (Brandenberger *et al.,* 2015).[12] Thus, protecting against both a non-severe and a reversible effect offers more flexibility in determination of appropriate conservatism *vis-à-vis* a target for the HQ.

Derivation of an Alternative Chronic ESL

Applying the same benchmark dose (BMD)approach to the data from Klonne *et al.* - based on the occurrence of distinct nasal and tracheal lesions at 2.3 ppm - produces a POD of 0.47 ppm for the $BDML_{10}$ and a chronic ReV of 2.8 ppb. This value is more in line with the chronic ESL established for HCl, but requires the use of HQ=1.0. Further adjusting for a HQ = 0.3, per TCEQ guidelines, results in a chronic ESL of 0.83 ppb. Although still significantly lower than the HCl value, this alternative value is more in line with the nature of the effects seen in the key study.

Summary

ACC agrees with TCEQ's choice of Klonne et al. (1987) as the key study for determining the chronic ReV and ESL for Cl_2, but disagrees with the conclusion that the study suggests a LOAEL of 0.1 ppm for nasal lesions. Consistent with the conclusions of the study authors, we believe that the study supports a NOAEL of 0.5 ppm for tracheal lesions that are more likely to be a precursor to the adverse pulmonary effects observed at higher concentrations. Using the data for tracheal lesions results in a chronic ReV of 2.8 ppb and a chronic ESL of 0.83 ppb.

I welcome the opportunity to discuss this information further. Please feel free to contact me at 202-249-6727 or at srisotto@americanchemistry.com.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

[12] Brandenberger C. *et al.* Inhalation exposure to ethylene induces eosinophilic rhinitis and nasal epithelial remodeling in Fischer 344 rats. *Chemico-Biological Interactions* 241:66-75 (2015).