Texas Commission on Environmental Quality Response to Public Comments Received on the May 2013 Proposed Methanol Development Support Document

The public comment period for the May 2013 Proposed Development Support Document (DSD) for methanol ended in August 2013. The Methanol Institute (MI) submitted comments on August 16, 2013. The Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by the MI to provide technical comments on the proposed DSD for methanol. The goal of the 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. A summary of comments from the MI is provided below, followed by TCEQ responses. The full comments are provided in Appendix 1. Comments on issues that suggest changes in the DSD are addressed whereas comments agreeing with TCEQ's approach are not. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

Upon further review, the DSD has been revised. The acute ReV and ESL for methanol have been revised by using a NOAEL of 203.5 ppm, instead of LOAEL, from the same key study as the POD. The effects (mild and transient subclinical nasal inflammation) observed in the Mann et al. (2002) study is more appropriately considered a lowest-observed-effect-level (LOEL). Accordingly, the acute ReV and ESL have been revised from 7,000 $\mu g/m^3$ (5,400 ppb) and 2,100 $\mu g/m^3$ (1,600 ppb) to 13,000 $\mu g/m^3$ (10,000 ppb) and 3,900 $\mu g/m^3$ (3,000 ppb), respectively. The chronic ReV and ESL have also been revised by replacing the key study from the NEDO (1987) rat study for the incidences of formation of nodes in the lungs to the Kawai et al. (1991) occupational study for nasal irritation. Accordingly, the chronic ReV and ESL have been revised from 2,200 $\mu g/m^3$ (1,700 ppb) and 660 $\mu g/m^3$ (510 ppb) to 7,200 $\mu g/m^3$ (5,500 ppb) and 2,100 $\mu g/m^3$ (1,600 ppb), respectively.

1. Comments on Acute ReV

Comment No. 1 (Page 2-3):

The MI commented that the DSD proposes an acute ReV of 7 mg/m3 based on acute respiratory irritation, based on subclinical (responses not detected by the subjects) changes in some biomarkers from a 4-hour acute exposure of 12 human volunteers exposed to 200 ppm. The analysis applies Haber's Assumption to convert the level causing effects at 4 hours to an estimated level that would cause an effect at 1 hour. This adjustment is arbitrary and has elements that are conservative and not conservative.

The MI further commented that TCEQ used Haber's Rule as modified to $C^n \times T$ = constant and chose an exponent (n) of 3, resulting in an adjusted 1-hour point of departure (POD_{ADJ}) of 323.04 ppm. If TCEQ had used Haber's original equation (i.e. n = 1), the POD_{ADJ} would have been 814 ppm. A justification of an n of 3 vs. 1 is not provided. The MI further commented that there should be no adjustment for duration of exposure included in TCEQ's data on acute respiratory irritation. Irritation is driven by concentration, not by cumulative exposure. Time is not a factor. If 200 ppm is irritating during 4 hours of exposure, it will be irritating during 1 hour of exposure.

TCEQ Response:

The TCEQ agrees with the MI's comment that respiratory irritation effects are only concentration dependent, so an exposure duration adjustment from 4 h to 1 h for the 4-h POD was not conducted. Thus, the 4-h POD of 203.5 ppm was used as a 1-h concentration POD_{ADJ}. Consequently, neither the Haber's Rule as modified to $C^n \times T = K$ nor an exponent (n) of 3 was applied. Section 3.1.5 of the DSD has been revised accordingly.

Comment No. 2 (Page 3):

The MI indicated that there is an inconsistency within the DSD for the concentration of methanol that causes respiratory irritation. The acute ReV derivation is based on a LOAEL of 203 ppm from a 4-hour exposure to human volunteers. The chronic ReV section cites the study of Kawai et al. (1991) which reported a LOAEL for nasal irritation of 459 ppm in factory workers exposed 7-8 hours per day for 0.3 to 7.8 years. Thus, the reported subchronic irritation level in humans is considerably higher than the reported acute irritation level.

TCEQ Response:

After a reevaluation of all five available acute human studies including the Mann et al. (2002) study, the TCEQ notices that a free-standing NOAEL ranging from 191 to 203.5 ppm for absence of subjective symptoms and/or neurobehavioral, neurophysiological and visual performance effects was identified from these studies. The effects (subclinical nasal inflammatory reactions), observed in the Mann et al. (2002) study, were mild and no subjective clinical irritations were detected. The observed effects level of 203.5 ppm, a lowest-observed-effect-level (LOEL), would be too conservative to be considered a LOAEL. Thus, consistent with other human studies, the level of 203.5 ppm was considered a NOAEL for absence of irritation and subjective symptoms and was used as the POD to develop the acute ReV (see Section 3.1.2.1.6)

Comment No. 3 (Page 3):

The MI further commented that the uncertainty factors applied to the POD_{ADJ} are excessive. Six biomarkers for irritation were assessed, as well as the individual's perception of irritation. None of the volunteers perceived irritation and only 2 of the 6 biomarkers were increased. TCEQ has chosen to call this a LOAEL, rather than an NOAEL. The response seems to be on the border between an adverse effect and not an adverse effect. Therefore, adding an uncertainty factor of 2 for adjustment of LOAEL to NOAEL is excessive. The MI also commented that the acute database for methanol is extensive. The database uncertainty factor (UF_D) of 3 is not justified. It should be 1. We believe that the overall uncertainty factor should be 10.

TCEQ Response:

The TCEQ agrees with the MI's comments. Since the POD/POD_{ADJ} of 203.5 ppm is a NOAEL not a LOAEL, a UF_{LOAEL} was not applied. For database uncertainty factor, since no more than two doses were administered in these human studies and only free-standing NOAELs were identified, a UF_D was necessary. However, a UF_D of 2, instead of 3, was used. The overall uncertainty factor of 20, instead of 30, was applied to the $POD_{HEC.}$ Accordingly, the revised acute ReV is 10 ppm, instead of 5.4 ppm.

Comment No. 4 (Page 3):

Finally, the MI commented that the proposed acute ESL is 10-fold lower than the currently proposed chronic level by EPA (IRIS proposal for RfC is 20 mg/m3). We also believe that the Acute ReV should be 32 ppm, not 5.4 ppm.

TCEQ Response:

The TCEQ appreciates the MI's comments. The DSD was not revised based on these comments. The TCEQ believes that the revised acute ReV of 10 ppm and ESL of 3 ppm, while lower than that recommended by the MI, would not be too conservative when used for reviews of ambient air monitoring data and air permit applications, respectively.

2. Comments on Chronic ReV

Comment No. 5 (Page 3):

The MI commented that the chronic ReV should not be based on the reporting of "nodes in the lungs" observed at gross necropsy in the chronic rat study of methanol by NEDO. The MI indicated that the primary purpose of gross necropsy is to identify potential lesions to be examined microscopically. When there is microscopic evaluation of tissues, the histopathologic evaluation should be used, not necropsy data. There is no definition of "nodes"; the original report was written in Japanese and translated. The original authors are not available to determine what was meant by nodes. Several pathologic conditions could be classified as nodes, although this is not a common term used in US pathology/toxicology studies. The histopathology identified several of these nodes as adenomas. The authors noted that the incidences of lung adenomas in all treatment groups were within the laboratory's historical control incidence and were judged not to be caused by methanol exposure. This finding should not be used for developing a ReV or ESL.

TCEQ Response:

The TCEQ agrees with the MI's comments. The NEDO (1987) chronic rat study for formation of nodes in the lung has been removed from the key studies section. However, the Kawai et al. (1991) occupational study and the NEDO (1987) two-generation reproductive/developmental study in rats remained in the key studies section.

Comment No. 5 (Page 3):

The MI indicated that EPA based its RfC on developmental toxicity in the Rogers et al. (1993) study. It suggested that TCEQ should use that study to develop a chronic ReV and ESL.

TCEQ Response:

The TCEQ appreciates the MI's comments. The DSD was not revised based on these comments. USEPA derived its RfC in 2013 based on developmental toxicities observed in the Rogers et al. (1993) study as well as in the NEDO (1987) study. A NOAEL (1,000 ppm) and LOAEL (2,000 ppm) for formation of cervical ribs in mice exposed to methanol during organogenesis (on gestation days (GD) 6-15) were identified from the Rogers et al. (1993) study. The NEDO (1987) study was a two-generation reproductive/developmental study with a NOAEL (500 ppm) and

LOAEL (1,000 ppm) for decrease in the brain weights in rats exposed to methanol from early gestation through 8 weeks of postnatal life were identified. A candidate RfC of 20 and 17.8 mg/m^3 were derived, respectively, based on the Rogers et al. (1993) study and NEDO (1987) study. The candidate RfC of 17.8 mg/m^3 based on the NEDO (1987) rat developmental study is lower than that based on the Rogers et al. (1993) study and was selected by USEPA as the RfC (20 mg/m^3, rounded to 1 significant figure) for methanol.

As described in Section A.2.2., Appendix A of the TCEQ DSD, the Toxicology Excellence for Risk Assessment (TERA 2011) has indicated that an increase in rudimentary and extra cervical ribs, as observed by Rogers et al. (1993), should not be considered indicative of developmental toxicity. Furthermore, the critical effects of decrease in brain weights observed in the NEDO (1987) studies were considered biologically significant and relevant to humans. Therefore, in addition to use a LOAEL of 459 ppm identified from the Kawai et al. (1991) occupational study, the POD identified from the NEDO (1987) two-generation rat study was used to develop a potential chronic ReV. The corresponding calculated POD_{HEC} from the POD identified by NEDO (1987) was 762.891 ppm. The POD_{HEC} of 762.891 ppm is above an inhalation concentration of 500 ppm, a level which is considered uncertain according to the human PBPK model developed for methanol by USEPA (2013a), since the blood levels predicted rise above those for which there are model calibration data. Furthermore, The POD_{HEC} of 762.891 ppm was higher than the POD_{HEC} of 163.93 ppm for nasal irritation based on Kawai et al. (1991) occupational study. Therefore, the POD_{HEC} of 163.93 ppm for nasal irritation was used to derive chronic ReV (Section 4.1.6 of the TCEQ DSD).

Comment No. 6 (Page 3):

The MI further suggested that TCEQ take into account that methanol is a constituent of normal metabolism and is present in the cells and blood of all humans, without exogenous exposure to methanol. It further indicated that the proposed chronic ESL would raise blood methanol less than 1% above the endogenous level. Finally, the MI commented that it does not make sense to set the ESL so low that exposure at that level would not even be distinguishable from the endogenous level in humans.

TCEQ Response:

The TCEQ appreciates the MI's comments. The DSD was not revised based on these comments. The TCEQ notices that methanol is a constituent of normal metabolism and is present in the cells and blood of all humans. As such, blood methanol concentration is more appropriate to be used as the internal dose metric for developmental/and reproductive effects. The chronic ReV was based on a critical effect of nasal irritation observed in workers (Kawai et al. 1991). Since the key study was based on workers, information on endogenous blood methanol and other more appropriate dose metrics were not available. In addition, the MOA for nasal irritation, a point of contact effect, was presumably attributed to the methanol metabolite, formic acid (Section 4.1.3.1). Therefore, methanol exposure concentration was directly used as POD.

The TCEQ also developed a potential chronic ReV for developmental effects based on the NEDO (1987) two-generation rat studies. The TCEQ then used the internal BMDL ($POD_{internal}$) estimated by USEPA to derive a potential chronic ReV for developmental/reproductive effects. Because the MOA for developmental/and reproductive effects was associated with methanol, not

formic acid and the estimated $POD_{internal}$ is above endogenous background, the estimated $POD_{internal}$ was adjusted by an endogenous background blood concentration set by USEPA. The corresponding POD_{HEC} of 762.891 ppm, however, is above an inhalation concentration of 500 ppm, a level which is considered uncertain according to the human PBPK model developed for methanol by USEPA (2013a), since the blood levels predicted rise above those for which there are model calibration data (Section 4.1.6.2). Furthermore, the estimated POD_{HEC} of 762.891 for developmental effect is much higher than that for nasal irritation based on the Kawai et al. (1991) occupational study (163.92 ppm). Thus, the POD_{HEC} for nasal irritation was selected to derive chronic ReV. The TCEQ believes that if the derived chronic ReV protects against critical effect of nasal irritation, reproductive/developmental effects will be protected (Section 4.1.8).

APPENDIX 1

The Methanol Institute

Comments Regarding the TCEQ Development Support Document for Methanol Toxicity Values

Methanol Institute

Comments on TCEQ Development Support Document for Methanol

CAS Registry Number: 67-56-1

August 16, 2013

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Methanol Institute's Comments
On the TCEQ Development Support Document for Methanol

As the trade association for the global methanol industry, the Methanol Institute (MI) welcomes this opportunity for public comment on the TCEQ Development Support Document (DSD) for Methanol. As you are no doubt aware, Texas is one of the main beneficiaries of the ongoing resurgence in domestic methanol production made possible by the abundant, low-cost natural gas available in the Gulf Coast region.

For example, Celanese Corporation, headquartered in Dallas and with 7,600 employees worldwide, and net sales of $6.4 billion in 2012, recently announced a joint-venture with Mitsui & Co. Ltd. to produce methanol at Celanese's integrated chemical plant in Clear Lake. This $800 million project, expected to produce 1.3 million tons of methanol annually, will have a strong economic impact on the surrounding area. Additionally, LyondellBassell, one of the world's largest plastics, chemical and refining companies, is proceeding with plans to reopen a 780,000 ton per year methanol plant at Channelview that was shuttered in 2003 due to high natural gas prices. When back on line, the company expects the plant to generate $130-150 million in revenue per year. Orascom Construction Industries (OCI) is completing a $100 million debottlenecking project at its methanol complex in Beaumont. This project will increase the complex's methanol capacity by 25%, to 875,000 tons per year. And on January 18, 2013, G2X Energy broke ground for a small 60,000 metric ton per year plant in Pampa. This one small plant is creating 300 construction jobs on a brownfield site, 40 permanent jobs, 21 jobs for transport, and is injecting $155 million into the local Texas economy. Taken together, these projects represent a significant number of new jobs and an expanded tax base for the State of Texas.

Upon completing a review of the DSD for methanol, we at the Methanol Institute have the following comments:

The DSD proposes an acute ReV of 7 mg/m3 based on acute respiratory irritation, based on subclinical (responses not detected by the subjects) changes in some biomarkers from a 4-hour acute exposure of 12 human volunteers exposed to 200 ppm. The analysis applies Haber's Assumption to convert the level causing effects at 4 hours to an estimated level that would cause an effect at 1 hour. This adjustment is arbitrary and has elements that are conservative and not conservative.

Haber's Assumption is based on cumulative exposure, such that the product of concentration and time is a constant. E.g., if exposure at 100 ppm for 1 hour causes some effect, then exposure at 50 ppm for 2 hours would cause the same effect. This has been shown to be inaccurate in many cases, so the equation has been modified to $C^n * T = \text{constant}$. The investigator chooses what value of "n" to use to either fit the existing data, or drive a regulatory decision. TCEQ chose a value of 3, resulting in an adjusted 1-hour point of departure (POD_{ADJ}) of 323.04 ppm. If TCEQ had used Haber's original equation (i.e. n = 1), the POD_{ADJ} would have been 814 ppm. A justification of an n of 3 vs. 1 is not provided.

Further, we feel that there should be no adjustment for duration of exposure included in TCEQ's data on acute respiratory irritation. Irritation is driven by concentration, not by cumulative exposure. Time is not a factor. If 200 ppm is irritating during 4 hours of exposure, it will be irritating during 1 hour of exposure.

Additionally, we believe there to be an inconsistency within the DSD for the concentration of methanol that causes respiratory irritation. The acute ReV derivation is based on a LOAEL of 203 ppm from a 4-hour exposure to human volunteers. The chronic ReV section cites the study of Kawai et al. (1991) which reported a LOAEL for nasal irritation of 459 ppm in factory workers exposed 7-8 hours per day for 0.3 to 7.8 years. Thus, the reported subchronic irritation level in humans is considerably higher than the reported acute irritation level.

We also believe that the uncertainty factors applied to the POD_{ADJ} are excessive. Six biomarkers for irritation were assessed, as well as the individual's perception of irritation. None of the volunteers perceived irritation and only 2 of the 6 biomarkers were increased. TCEQ has chosen to call this a LOAEL, rather than an NOAEL. The response seems to be on the border between an adverse effect and not an adverse effect. Therefore, adding an uncertainty factor of 2 for adjustment of LOAEL to NOAEL is excessive.

Furthermore, the acute database for methanol is extensive. The database uncertainty factor of 3 is not justified. It should be 1.

We believe that the overall uncertainty factor should be 10.

The proposed acute Effect Screening Level (ESL) is 10-fold lower than the currently proposed chronic level by EPA (IRIS proposal for RfC is 20 mg/m^3)

We also believe that the Acute ReV should be 32 ppm, not 5.4 ppm.

The Chronic ReV is based on the reporting of "nodes in the lungs" observed at gross necropsy in the chronic rat study of methanol by NEDO. The primary purpose of gross necropsy is to identify potential lesions to be examined microscopically. When there is microscopic evaluation of tissues, the histopathologic evaluation should be used, not necropsy data. There is no definition of "nodes"; the original report was written in Japanese and translated. The original authors are not available to determine what was meant by nodes. Several pathologic conditions could be classified as nodes, although this is not a common term used in US pathology/toxicology studies. The histopathology identified several of these nodes as adenomas. The authors noted that the incidences of lung adenomas in all treatment groups were within the laboratory's historical control incidence and were judged not to be caused by methanol exposure. This finding should not be used for developing an ReV or ESL.

EPA based its RfC on developmental toxicity in the Rogers et al. study. We feel that TCEQ should use that study to develop an ESL. In developing a chronic ReV and ESL, TCEQ needs to take into account that methanol is a constituent of normal metabolism and is present in the cells and blood of all humans, without exogenous exposure to methanol. The proposed chronic ESL would raise blood methanol less than 1% above the endogenous level. It does not make sense to set the ESL so low that exposure at that level would not even be distinguishable from the endogenous level in humans.

Once again, the Methanol Institute appreciates the opportunity to provide comments to the TCEQ Development Support Document for Methanol. We look forward to remaining engaged with the TCEQ as the process moves forward.

Sincerely,

Gregory Dolan
Acting CEO