

## **Texas Commission on Environmental Quality Response to Public Comments Received on the September 2008 Proposed Silica Development Support Document**

The public comment period for the September 2008 Proposed Development Support Document (DSD) for silica ended in January 2009. The Association of Electric Companies of Texas, North American Insulation Manufacturers Association, and American Chemistry Council's Crystalline Silica Panel, submitted comments. The Toxicology Division (TD) of the Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by these organizations to provide technical comments on the proposed DSD for silica. The goal of the TD 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. A summary of comments from each organization is provided below, followed by TCEQ responses. The full comments are provided in Appendices A, B, and C. Comments on issues that suggest a change 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 and limited to crystalline forms of silica. The TD will develop ESLs for amorphous and other non-crystalline forms in a separate DSD at a later date. The acute ReV and ESL for crystalline silica have been revised by adjusting the POD by a ratio of 54/30 to reflect 54% content of quartz as opposed to 30% of the respirable dust exposure for the cohort in the Hnizdo et al. (1993) study.

### **Association of Electric Companies of Texas (AECT)** **(Appendix A)**

1. **Comment:** AECT stated that it appreciates that the TCEQ followed a methodical, scientific process in developing the proposed DSD for silica. In particular, the process included a scientific technical evaluation conducted by the Toxicology Excellence for Risk Assessment ("TERA"). AECT believes that such process has resulted in proposed silica ESLs that are more scientifically supportable and appropriate than the current interim ESLs.

**TCEQ Response:** The TD appreciates AECT's support for the proposed revised silica ESLs and DSD and acknowledgment that the TCEQ has provided scientifically supportable and appropriate ESL values for silica.

### **North American Insulation Manufacturers Association (NAIMA)** **(Appendix B)**

2. **Comments on Pages 2-3:** NAIMA commented that the proposed DSD for silica makes a contrary and wholly unscientific "policy decision" to treat all forms of silica alike. NAIMA indicated that the proposed DSD does not fully discuss all of the classifications and regulations of silica currently in place which consistently distinguish between crystalline and amorphous silica. NAIMA urges that the proposed DSD should recognize the difference between crystalline and amorphous silica for hazard and risk purposes and focus its proposal on the crystalline forms of silica. NAIMA urges the TCEQ to acknowledge this distinction to avoid possible regulation of amorphous silica under the

**TCEQ Response:** The TD agrees that it is more appropriate to set ESL values for amorphous and other non-crystalline forms of silica in a separate DSD. Accordingly, the proposed DSD has been revised and limited to crystalline forms of silica. The TD will develop ESLs for amorphous and other non-crystalline forms in a separate DSD at a later date.

### **American Chemistry Council's Crystalline Silica Panel (ACC) (Appendices C and D)**

ACC provided a cover letter, with summaries of main comments (Appendix C), and an attachment containing detailed comments from Dr. Louis Anthony Cox, Jr (Appendix D). The majority of the comments in the cover letter were similar to the more detailed comments from Dr. Cox. So responses to these summary comments will be provided in responses to Dr. Cox's detailed comments. However, there was one comment that was included in ACC's cover letter that did not appear in Dr. Cox's comments and will be addressed first.

3. **Comment in ACC cover letter (bottom of Page 2 through Page 3):** In the DSD, the TCEQ calculates a chronic Reference Value and a chronic non-cancer ESL based on data from what it terms the "key study" of South African gold miners by Hnizdo et al. (1993) . . . In doing so, the TCEQ uses estimates of cumulative (respirable) dust exposure . . . and assumes . . . an average quartz content of 30%, as stated in the paper by Hnizdo et al. (1993). . . . There is a significant problem with this approach . . . because the quartz content of the incinerated and acid-treated dust would have been approximately 54%, rather than the 30% value found before incineration/acid treatment (Gibbs and Du Toit 2002).

**TCEQ Response:** The DSD has been revised to multiply the POD, which is the  $BMCL_{01}$ , by a ratio of 54/30 (1.8). The revised ReV value has been increased from  $1.1 \mu\text{g}/\text{m}^3$  to  $2.0 \mu\text{g}/\text{m}^3$ .

4. **Comment in ACC cover letter (bottom of Page 3):** In sum, when combined with other factors – such as the unrealistic assumption that dust levels did not change between 1936 and 1960 – the values presented in Hnizdo et al. (1993) and used by the TCEQ are likely to underestimate the actual quartz exposures of the miners in this cohort by a factor of 2. See Gibbs & De Toit (2002). While we do not know the precise impact this underestimation of exposures had on the TCEQ's risk assessment, preliminary analyses performed by others suggest that the impact is likely to have been very substantial, resulting in a large overestimate of risk.<sup>5</sup> (footnote 5 = See Gibbs & Du Toit (2002) at 602; Hughes, JM. Radiographic Evidence of Silicosis in Relation to Silica Exposure (1995) . . . (noting that a twofold underestimation of exposure in the Hnizdo et al. (1993) cohort "could account for more than a tenfold overestimation in risk").

**TCEQ Response:** The DSD was not revised based on this comment. The Statement made by Hughes (1995) that "because **the shape of the dose response curve**, a twofold underestimation could account for more than tenfold overestimation of risk" (emphasis

added) is correct for the cumulative risk of silicosis given in Figure 1 (Figure 2 of Hnizio and Sluis-Cremer, 1993). That would be an issue if the model were to be used to estimate risks to a different population with different exposure levels. However, what Hughes (1995) does not discuss is how a point of departure changes with a proportional change in the cumulative dust dose ( $\text{mg}/\text{m}^3\text{-years}$ ). That is, how does the cumulative dust dose ( $\text{mg}/\text{m}^3\text{-years}$ ) corresponding to a specified extra risk change with a proportional change in the cumulative dust dose ( $\text{mg}/\text{m}^3\text{-years}$ ). The answer is that the proportional change in the POD is identical to the proportional change in the dose metric.

Since TCEQ is using the Hnizio and Sluis-Cremer (1993) data to estimate a POD, then the POD changes by exactly the same proportion that the dose changes. In addition, had TCEQ not adjusted the POD to reflect 54% content of quartz as opposed to 30%, the “overestimation” of risks due to environmental exposures below the POD would have been equal to a factor of 1.8.

Comments were submitted for ACC from Dr. Louis Anthony Cox, Jr. in a separate document (Appendix D).

- 5. Comment #1 on Page 1:** *No well-developed hazard identification.* The DSD assumes that exposures to the various forms of silica at concentration that do not exceed  $0.1 \text{ mg}/\text{m}^3$  can cause lung cancer and other adverse health effects . . .

**TCEQ Response:** The weight-of-evidence section and mode of action section have been revised and expanded to include a discussion of both a potential nonlinear, threshold mode of action and a potential linear, nonthreshold model of action. In addition, a discussion on whether silicosis is necessary for the development of lung cancer has been included. *There is not a consensus among the scientific community on whether the carcinogenic MOA for silica is nonlinear or linear or whether silicosis is necessary for the development of lung cancer.*

- 6. Comment #2 on Page 1:** *Definition of adverse effect and POD.* TCEQ defines “inflammation,” apparently meaning recruitment of alveolar macrophages and neutrophils into the lung to help clear particles, as an adverse effect . . . We therefore believe that the POD should not be based on such normal, transient “inflammatory” events, but rather on pathological changes or their precursors, such as improper repair of damaged lung tissue, scarring, or fibrosis.

**TCEQ Response:** The DSD was not revised based on this comment. The TD disagrees with ACC’s recommendation that the TD use fibrosis, rather than delayed recruitment of neutrophil and increased BALF LDH, as the critical effects. Silica is known to produce pulmonary inflammation during the acute phase and consequently develops silica-induced fibrosis during the chronic phase. Acute silicosis results from exposure to relatively high levels of silica with an onset of 1-3 year. There is little data available regarding the pulmonary toxicity caused by short-term inhalation of silica, and no studies thus far report that short-term exposure of low levels silica produces fibrosis. Thus, using fibrosis as the critical effects to develop acute toxicity factors is not applicable. Furthermore, “persistent, unresolved inflammation” is not an acute effect, so it cannot be considered for the acute ESL. However, short-term inflammation and cytotoxicity are precursors to persistent, unresolved inflammation and therefore appropriate as a POD.

The TD believes that it is appropriate to use delayed recruitment of neutrophil and increased BALF LDH, as the critical effects for developing the acute ReV and ESL.

7. **Comment #3 on Page 2:** *There is no evidence that amorphous silica poses a human health risk. We strongly disagree that exposures to non-crystalline silicas should be treated similarly or identically to exposures to crystalline silica. . .*

**TCEQ Response:** The TD agrees that it is more appropriate to set ESL values for amorphous and other non-crystalline forms of silica in a separate DSD (see response to Comment No. 2).

8. **Comment #4 on Page 2:** *The particle size-dependency of toxicity for crystalline silica is not treated correctly.*

**TCEQ Response:** Section 4.1.1 *Physical/Chemical Properties and Key Studies* has been revised to acknowledge that nanosized particles probably pose less risk of fibrosis. However, during the air permit review process, information on nanosized particles is not available. The TD assumes that the typical portion of nanosized particles is minimal relative to the non-nanosized particles and is included in the modeled respirable silica emissions for air permits.

9. **Comment #5 on Page 2:** *Using point estimates of cumulative exposures (mean or total), while ignoring the variance of true exposures around the estimated values, biases potency estimates upward. TCEQ should correct its potency estimates for this source of bias.*

**TCEQ Response:** The DSD was not revised based on this comment. ACC's claim that Steenland et al. (2001) used point estimates of cumulative exposure in the estimation of slopes is very likely correct. However, the claim that the slope estimates are biased high as a result of not accounting for the variability in the exposures is not warranted. First, there are no references that support their claim that the potency estimates are "biased upward" when point estimates of cumulative exposures are used in dose-response modeling. Second, the claim that "silicosis and lung cancer cases are expected to occur disproportionately and perhaps exclusively among individuals with greater-than-estimated exposures" is purely speculative and has no scientific basis whatsoever. Third, there are documented cases which indicate the opposite effect than the effect claimed by ACC reviewers. For example, Stayner et al. (2003) found that "occupational cohort mortality studies have observed exposure-response curves to have an increasing slope at low exposure levels that attenuates or even turns negative at high exposure levels. Examples discussed in this paper include dioxin, **silica**, ..." (emphasis added).

References:

Stayner, L, K. Steenland, M. Dosemeci, I. Hertz-Picciotto (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scandinavian Journal of Work, Environment & Health*, 29:317-324.  
Steenland, K. (2005). Editorial: Smoothing is Soothing, and Splines are Fine. *Occupational and Environmental Medicine*, 62:141-142.

10. **Comment #6 on Page 3:** *TCEQ has not documented any effects of silica exposures on lung stem cells involved in the development of lung cancer.*

**TCEQ Response:** The DSD has been revised to discuss the potential role of alveolar type II cells (stem cells or progenitor cells that divide and differentiate into type I cells) in the development of lung cancer (see Section 4.2.1.2 *Animal Studies* of the revised Silica DSD).

11. **Comment #7 on Page 3:** *TCEQ's use of Steenland et al. (2001) as a key study does not correct for model specification errors and biases in Steenland et al.'s analysis*

**TCEQ Response:** The DSD was not revised based on this comment. ACC's claim does not have any statistical basis. ACC cannot prove independence between exposure and lung cancer mortality among workers exposed to silica. We cannot prove dependence because we do not have the raw data. Something that can be observed, though, in Steenland et al. pooled analyses is that all ten individual studies in the pooled analysis result in positive slopes, indicating that lung cancer mortality increases with increasing cumulative exposure to silica. In addition, four of the associations (i.e., slopes) using the log-linear model with cumulative exposure lagged 15 years are statistically significant at the 5% significance level. ACC dismissed the fact that the positive association between cumulative exposure and lung cancer mortality is statistically significant in some of the studies.

With respect to "model specification errors and biases" there is no known/standard test or method to "correct" for model specification. The scientific community agrees that parsimonious models (e.g., linear or log-linear multiplicative relative risk models) are to be preferred over other less-plausible models. If there is biological information that allows for a biologically-based model, then that model would be preferable. ACC's suggestion of using a biologically-based model is the best scientific recommendation that can be given in general. However, the scientific mechanism and scientific biological information of how silica causes cancer is not definitively known.

12. **Comment on bottom of Page 3 through page 5:** *Definition of "critical effect."* The ACC commented that it is not appropriate to define critical effects of acute exposure to silica as increased inflammation and cytotoxicity in the respiratory tract (Page 6, line 36 of proposed DSD). ACC argued that increased markers of inflammation and cytotoxicity (such as macrophage activation and neutrophil recruitment) in respiratory tracts in response to particulate exposures do not necessarily indicate a pathological state or any harm or injury. To the contrary, in the lungs, many aspects of transient inflammation and cytotoxicity may simply be biomarkers of exposure and not adverse effects, but a normal and expected part of homeostasis for animals in non-sterile environments. Therefore, the use of exposures that cause such inflammatory responses as a point of departure (POD) for risk assessment calculations is not appropriate. ACC believes that the POD should not be based on such normal, transient inflammatory events, but rather on pathological changes or their precursors, such as improper repair of damaged lung tissue, scarring, or fibrosis. ACC recommended that the TD redefine the critical effect as an unhealthy or adverse response (such as persistent, unresolved inflammation), or as a precursor condition that progresses to an adverse response, rather than as a normal, healthy response (transient inflammation and cytotoxicity as part of normal clearance of particulate matter from the lungs).

**TCEQ Response:** See response to comment No. 6.

13. **First Comment on Page 5:** *Use of unvalidated animal models.* The ACC commented that Chapter 3 of the DSD does not present any evidence that rats provide a valid animal model for human silicosis. It stated that before using an animal (e.g., rat) model as a basis for risk analysis of human health, it should be validated for such use by showing that the animal and human disease models share relevant mechanisms and responses. ACC recommended that the DSD add a discussion of the validity of the rat response to crystalline silica exposures, as a model for human responses.

**TCEQ Response:** Section 3.1.2 of the DSD has been revised to include statements and references that rats are a valid animal model for human silicosis. Dr. Cox cited Wright et al. (2008) as evidence that rats are an unvalidated animal model. However, the Wright et al. (2008) article deals with mechanisms involved in the genesis of chronic obstructive pulmonary disease (COPD) (i.e., emphysema, small airway remodeling, pulmonary hypertension, and chronic bronchitis), not silicosis.

14. **Second Comment starting on the bottom of Page 5:** *Assigning one toxicity factor to different forms of silica undermines the basis for rational and effective health protection and risk management.* The ACC commented that there is no evidence that amorphous silica poses a human health risk. ACC strongly disagreed that exposures to non-crystalline silica should be treated similarly or identically to exposures to crystalline silica. ACC indicated that there are no epidemiological, toxicological, mechanistic, or other scientific grounds for treating amorphous silica as toxic or carcinogenic, or for assuming that it has the same toxic or carcinogenic potency factors as crystalline silica. ACC further commented that no credible data indicate that current exposures to amorphous silica cause any human health harm whatsoever.

**TCEQ Response:** Please see Response to Comment No. 2 above.

15. **Comment on bottom of Page 6:** *Non-sequitur reasoning.* The ACC commented that the passage "...[N]atural amorphous silica may contain up to 60% crystalline silica by weight. Therefore, the toxicity values developed in this document apply to crystalline and amorphous silica and their byproducts." (Page 7, lines 13-15 of the proposed DSD) does not seem to be logically justified.

**TCEQ Response:** While the TD may not necessarily agree with the comments, the TD does appreciate ACC's comments. Please see Response to Comment No. 2 above. The passage referred to in this comment has been removed from the crystalline silica DSD and a separate DSD will be developed for natural amorphous silica.

16. **Comment on Page 7:** *Important particle transport and size factors affecting cytotoxicity have been omitted.* The ACC commented that the particle size-dependency of toxicity for crystalline silica is not treated correctly. TCEQ's proposal should be revised to reflect the fact that sufficiently fine (nanosized) particles probably pose less risk of fibrosis (and resulting harm) than larger particles – due to the fact that they are more readily diffused and translocated. The ACC commented that the assumption that the same acute toxicity factor will apply to all silica particles less than or equal to 10  $\mu\text{m}$  (PM<sub>10</sub>) (Page 7, lines 17-23 of the DSD) does not appear to be well supported by available evidence. The ACC indicated that it has been demonstrated experimentally that sufficiently small silica particles have significantly less toxicity than larger ones in causing lung fibrogenesis

**TCEQ Response:** The TD acknowledges that only a restricted range of SiO<sub>2</sub> particle sizes (neither too large nor too small) causes this critical effect in rats. However, in the absence of comprehensive data on the silica-induced effects of different particle sizes, it is not possible to adjust the acute toxicity factors for different particle size distributions. The mass median aerodynamic diameter (MMAD) for silica administered to the inhalation studies (Warheit et al. 1991, 1995), which were based to derive the acute ReV and ESL, were 3.7 μm (δg = 1.5), with greater than 97% of particles less than 10 μm in size. Therefore, the TD set the silica's acute toxicity factors specifically for all particles less than 10 μm. It has been a general practice by US EPA, OSHA and other regulatory agencies to regulate particles either as course (PM<sub>10</sub>), respiratory (PM<sub>4</sub>), or fine (PM<sub>2.5</sub>) and to consider all particles less than these cut-off points to be included in these ranges.

17. **Recommendation of Page 7:** ACC recommended that the TD uses fibrosis, rather than delayed recruitment of neutrophil and increased BALF LDH, as the critical effect.

**TCEQ Response:** See response to comment No. 6.

18. **First Comment on Page 8:** *Criteria for “overly conservative” are not stated.* (p. 14. lines 29-32. “Although the lack of nodular fibrosis and reduced pulmonary function following exposure to amorphous precipitated silica may indicate that its toxicity is not as great as other forms of silica, TD believes the application of the chronic toxicity factor derived from quartz to all forms of silica is not overly conservative.”) The ACC commented that the TD's policy decision to apply one set of acute toxicity factors to all forms of silica undermines the basis for rational and effective health protection and risk management.

**TCEQ Response:** Although the TD does not necessarily agree with ACC's comments that amorphous silica at current exposure levels shows no evidence of toxicity, the TD will develop toxicity factors for amorphous silica in a separate DSD. Please also see Response to Comment No. 2 above.

19. **Second Comment on Page 8 through Page 9:** P. 15, lines 39-40. Cumulative dust exposure was calculated up to the onset of silicosis or the end of exposure . . . )  
*Cumulative dust exposure has not been validated as the exposure metric that best predicts risk, . . .*

**TCEQ Response:** The DSD was not revised based on this comment. There are several concerns raised by the ACC in this comment concerning the chronic noncarcinogenic assessment for silica, although the TCEQ response contains information on the use of cumulative dust exposure for both the noncarcinogenic and carcinogenic assessments.

1. ACC is concerned that cumulative exposure may not be the correct dose metric. ACC cites literature where it was found that cumulative exposure to low concentrations of diesel was not the best dose metric for predicting responses in rats. The article cited by ACC found that lung burden from high concentrations of diesel was a better predictor of the responses observed in rats. The article is very interesting and shows that lung burden from exposures to high concentrations of diesel are better predictors of the responses observed in rats than cumulative exposures to diesel. ACC, however, fails to indicate how this knowledge about the effects and mechanism of action of diesel exposure in rats can

be used to estimate the mechanism of action of silica exposures in humans. Even further, it is not clear (and there is no scientifically-based method without more information and the full epidemiological data) how all this mechanistic data and analyses done in rats exposed to diesel can be used to modify the maximum likelihood estimate of a model parameter based on epidemiological data of workers exposed to silica.

2. ACC's claim that the Steenland et al. 2001 paper used point estimates of cumulative exposure in the estimation of slopes is very likely correct. However, the claim that the slope estimates are biased high as a result of not accounting for the variability in the exposures is not warranted. First, there are no references that support their claim that the potency estimates are "biased upward" when point estimates of cumulative exposures are used in dose-response modeling. Second, the claim that "silicosis and lung cancer cases are expected to occur disproportionately and perhaps exclusively) among individuals with greater-than-estimated exposures" is purely speculative and has no scientific basis whatsoever. Third, there are documented cases which indicate the opposite effect than the effect claimed by ACC reviewers. For example, Stayner et al. (2003) found that "occupational cohort mortality studies have observed exposure-response curves to have an increasing slope at low exposure levels that attenuates or even turns negative at high exposure levels. Examples discussed in this paper include dioxin, **silica, ...**" (**emphasis added**).

3. The ACC recommends using the central limit theorem as a way to assume a normal distribution for the cumulative exposure. Although this is an appropriate theoretical recommendation applicable to a wide range of situations, in practice using the central limit theorem is not always possible with cumulative exposures. It may be applicable if, a) the data are available, b) the exposure levels from one exposure period to another are independent (which is almost never the case), and c) the exposure levels have the same distribution (which is hardly ever the case).

References:

Stayner, L, K. Steenland, M. Dosemeci, I. Hertz-Picciotto (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scandinavian Journal of Work, Environment & Health*, 29:317-324.  
Steenland, K. (2005). Editorial: Smoothing is Soothing, and Splines are Fine. *Occupational and Environmental Medicine*, 62:141-142.  
Etc.

20. **Comment on Page 9: Incorrect MOA.** The ACC commented that the TD's treating chronic inflammation as the MOA for silicosis/fibrosis associated with long-term silica exposure (Page 16, lines 31-32 of the DSD) is incorrect. ACC indicated that chronic inflammation itself is not a primary mechanism of fibrosis; it may be necessary, but is not sufficient. Rather, improper repair of damaged lung tissue (such as degradation of collagens in the ECM due to sustained disruption of protease-antiprotease balance) is essential for fibrosis. Exposures that cause chronic inflammation but not improper repair of damage to lung tissue should not be expected to cause fibrosis.

**TCEQ Response:** The TD has modified the MOA for silicosis/fibrosis associated with long-term silica exposure (Section 4.1.2 of the DSD).

21. **Second Comment on page 9:** p. 17, lines 26-27: "Therefore, the model with the lowest AIC value (log-probit) was selected as the best fitting model." Recommendation: Use

**TCEQ Response:** The DSD has been revised to include information on potential model uncertainty. However, Bayesian model averaging (BMA) is a technique used to determine a point estimate out of several different point estimates. BMA does require some assumptions and there is no general consensus that this is the best method of eliciting an estimate. The BMA is more useful when there are large differences between model parameter estimates. There are several other methods that can be used to determine the best model estimate out of several different model estimates. BMA is one of them, Bayesian information criterion (BIC), Akaike information criterion (AIC), etc. All these methods emphasize different aspects of the models when eliciting a single estimate out of several alternatives. Some regulatory agencies, e.g., EPA, often opt for choosing the model that is most protective of human health. The TD, however, used the AIC to determine the best estimate of the benchmark dose for silica in the study based on Hnizdo.

There is little difference between  $BMCL_{01}$  values from the different models in Table 4. The values range from  $0.422 \text{ mg/m}^3\text{-yr}$  (highest AIC) to  $0.635 \text{ mg/m}^3\text{-yr}$  (lowest AIC) implying that the difference between the largest or smallest estimate in Table 4 and the best parameter that can be estimated from those four points is less than a factor of 1.5. The ratio between the  $BMC_{01}$  and  $BMCL_{01}$  for all models were less than 1.2 fold. This indicates model uncertainty is low. The scaled residuals at the estimated response closest to the  $BMR_{01}$  from the log-probit model were much lower than the other models, so it is clear that the log probit model was the preferred model.

22. **Numerous Comments starting at the bottom of Page 9 through Page 12:** *Improper application of cancer risk assessment to a non-carcinogen in the absence of evidence of carcinogenicity. . . . The decision to treat amorphous silicas as carcinogenic is not justified by a valid appeal to “conservatism”. The TS’s decision to apply the same chronic  $ES_{linear(c)}$  to all forms of silica is inconsistent with biological knowledge. . . . The decision to treat amorphous silica as carcinogenic is not justified by data or biological evidence. . . .*

**TCEQ Response:** The TCEQ agrees that there are insufficient data to classify amorphous silica as a carcinogen and acknowledges that consideration of amorphous silica in the section on carcinogenesis was conservative in the proposed DSD. The proposed DSD has been revised and limited to crystalline forms of silica, and the TD will develop ESLs for amorphous and other non-crystalline forms in a separate DSD at a later date.

23. **Comments on Page 12 through Page 14:** (p. 22, lines 43-44. “While a detailed carcinogenic MOA for silica is not available, several potential MOAs exist, including direct genotoxicity and cell proliferation secondary to chronic inflammation.”) *The TS’s suggested “potential MOAs” appear to be very general speculations, not specifically addressing, or appropriate for, lung carcinogenesis and silica.*

**TCEQ Response:** The MOA section has been revised and greatly expanded to include a discussion of the potential MOA for a nonlinear dose-response relationship as well as a linear dose-response relationship. Section 4.2.1.2 *Animal Studies* has been included in the revised DSD to discuss the development of epithelial hyperplasia in alveolar type II

cells (stem cells or progenitor cells that divide and differentiate into type I cells) and lung tumors in a rat model. *The scientific community does not agree on the key steps involved in the carcinogenic MOA of silica.*

ACC suggests using a biologically-based model for carcinogenicity of silica. The use of biologically-based models should be the ultimate goal of any carcinogenic model. However, as implicitly indicated by Cox's first sentence in his referenced paper "**If** a specific biological mechanism could be determined by which a carcinogen increases lung cancer risk, how might this knowledge be used to improve risk assessment?" (emphasis added) biological knowledge of the mechanism of cancer formation for a specific carcinogen is lacking or at best very limited. Cox then adds in his publication that to build these biologically-based models "it is necessary to have enough knowledge to build a model linking exposures to biological responses—often a challenge."

24. **Comments on Page 14 through Page 16:** (p. 23, lines 20-21. "However, more recent evidence indicates that silicosis is not a risk factor for lung cancer.") *This is an incorrect and highly selective interpretation of the cited sources, and it runs counter to the preponderance of scientific evidence, which indicates that silicosis likely is a necessary risk factor for silica-related lung cancer. The TS has cited only three studies (Checkoway et al. 1999, Chen and Chen 2002, and Yu et al. 2007) to support its claim that silicosis (for which there is an exposure threshold) is not a risk factor for lung cancer in silica-exposure worker – the implication being that exposure to silica dust (without an exposure threshold) is a risk factor for lung cancer independently of silicosis. . . .*

**TCEQ Response:** The DSD has been revised to include (1) a discussion of epidemiological evidence including the Pelucchi et al. (2006) and Errand et al. (2008) studies and (2) mode of action information to support whether silicosis is or is not a risk factor for lung cancer (Section 4.2.1 Weight-of-Evidence and Section 4.2.2 MOA Analysis). The results from the Jin et al. (2008) study are interesting and have been included in Section 4.2.1.2 *Animal Studies*.

There are a number of Dr. Cox's comments that suggest the data are clear that "potential silica-related lung cancer occurs only in the presence of silicosis". However, this is not the case. This subject is being actively investigated and there are inconclusive data, and as a consequent, varying opinions amongst epidemiologists and other scientists. In fact, the role of silicosis in lung cancer is likely to remain controversial (Checkoway and Franzblau 2000).

In 2006, Pelucchi et al. reviewed epidemiological studies from 1996-2005 and analyzed occupational silica exposure and lung cancer risk. However, there was only one cohort study (Checkoway et al. (1999) Thorax 54: 56-59) and a case control study (Ulm et al. (1999 Thorax 1999) where data on non silicotic subjects were available and the studies were deemed acceptable. They concluded:

"In this re-analysis, the association with lung cancer was consistent for silicotics, but *the data were limited for non silicotic subjects* (italics added for emphasis only) and not easily explained for undefined silicosis status workers. This leaves open the issue of dose-risk relation and pathogenic mechanism and supports the conclusion that the carcinogenic role of silica per se in absence of silicosis is still unclear."

In 2008, Erren et al. conducted a meta-analytical approach to determine “Is exposure to silica associated with lung cancer in the absence of silicosis?” These investigators identified 11 potential studies where data on non silicotic subjects were available. After his analysis, Erren et al. (2008) concluded

“But as for the main issue, the hypothesised association between lung cancer and exposure to silica in the absence of silicosis, our efforts *have failed to resolve the matter unambiguously.* (italics added for emphasis only) The summary RRs based on the 11 relevant studies did suggest a 20% increased risk, but differences between study-specific results were not easily attributable simply to sampling variability. . . . It follows that, even after deploying sophisticated statistical tools on apparently relevant epidemiological studies conducted to-date, *we were not able to answer the question:* (italics added for emphasis only) is exposure to silica associated with lung cancer in the absence of silicosis?”

25. **Comments on bottom of Page 16 through Page 17:** ( p. 23, lines 29-30. Steenland et al., (2001) pooled exposure-response data from ten of these studies.) *Steenland et al., pooled exposure estimates, not exposure data.* It is misleading to state that Steenland et al., pooled exposure-response data, when what they really did was to use retrospective estimates of exposure. . . .

**TCEQ Response:** The sentence “Steenland et al., (2001) pooled exposure-response data from ten of these studies” has been revised to “Steenland et al. (2001) pooled exposure-response analysis of ten of these studies.”

26. **Comments on bottom of Page 16 through Page 17:** From a statistical standpoint, this makes an important difference, because unmodeled errors in exposure estimates can create apparently “significant” associations between estimated exposure and response variables, even when there is no true relation between them, and even if the absence of a significant relation would be obvious if actual measurements (.data.) were used. . . .

Steenland et al. wrote that the exposure estimates were reasonably successful in estimating exposure, in as much as a positive and reasonably monotonic exposure-response trend was observed for silicosis mortality (quoted on p. 22, lines 43-35 of the DSD). However, both the mean and the error variance of estimated cumulative exposures (but not the variance of actual cumulative exposures, which is zero) increase with increasing exposure duration. Therefore, a positive monotonic trend could occur even if silica plays no role, or if the true dose-response relation has a concentration-and-duration threshold. Observing such a trend does not discriminate among alternative risk models (e.g., threshold vs. non-threshold) or establish that silica exposure, rather than age and duration in the work place, increase the risk of lung cancer.

**TCEQ Response:** The DSD was not revised based on this comment. ACC is correct in indicating that Steenland et al. used estimates of exposure instead of actual exposure (just like all models based on epidemiological data). That is, the ACC comment applies to all epidemiological studies that have been published in the literature and that will be published in the future (probably except for some epidemiological studies of individuals exposed to radiation that are measured with devices attached to exposed individuals –

although they are still estimates). ACC is also correct in indicating that the exposure estimates have a mean and an error variance. Again, this comment by ACC implies that any modeling effort of epidemiological data is useless unless the true exposure is known with no error. ACC fails to acknowledge that using that logic essentially invalidates any efforts of dose-response modeling and risk assessment, because at the end, it is not even the exposure that is relevant, but the actual, unknown, biological reactions (that are variable and uncertain) that cause the final effects. ACC's comments also invalidate risk assessments of every substance available because all of them are based on "estimates" and none of them, to our knowledge, are based on deterministic models with perfect information. Thus, although ACC comments about "estimates" not being equal to the true exposure because estimates contain errors are true, their comments do not offer a better alternative and their comments cannot be applied to the published pooled analysis by Steenland et al.

Another point made by ACC (they probably referred to DSD's page 23 lines 43-45 not p. 22, lines 43-35) refers to the estimates of exposure using silicosis as the endpoint. ACC may have also misunderstood that the quote "...the exposure estimates were reasonably successful in estimating exposure, in as much as a positive and reasonably monotonic exposure-response trend was observed" came from Steenland et al. This quote actually came from 't Mannetje et al. (2002). In this article, the aim of the authors was to study the relation between exposure to crystalline silica and silicosis mortality.

ACC also observes a well-known and obvious fact that cumulative exposures (estimated and actual) increase with increasing duration. ACC also indicates that the error variance of the estimated cumulative exposure increase with increasing duration (though they do not cite any references for this statement). There are published papers that conjecture that the error variance of cumulative exposure may be larger for larger cumulative exposures (due to job misclassification, exposure misclassification, exposure errors, measurement errors, etc.) However, there are no documented reports that indicate that the error variance of cumulative exposure increase with duration of exposure. For example, a worker could be exposed to a very low concentration of silica for 40 years and the cumulative exposure and the error variance may be small. Another worker, however, may be exposed to very high concentrations of silica for 5 years and the cumulative exposure and the error variance may be large. Thus, longer durations of exposure for different workers do not necessarily imply larger estimates of the cumulative exposures and larger error variances of the estimates.

ACC also makes the comment "Observing such a trend does not discriminate among alternative risk models (e.g., threshold vs. non-threshold) or establish that silica exposure, rather than age and duration in the work place, increase the risk of lung cancer." Here ACC is correct that a trend test does not discriminate between threshold and non-threshold model – a claim never made by Steenland et al. or TCEQ. The second part of ACC comments indicating that a positive trend does not necessarily prove causality is also true. However, the "rather than age and duration of work" part may be motivated by a lack of understanding of epidemiological dose-response modeling. The Cox-proportional hazards model adjusts for the effects of age on the increasing hazard rate of lung cancer (i.e., age is used as the index variable to form risk sets in the evaluation of the likelihood). This adjustment for age (in words for clarity) removes the effect that age has on the hazard rate of lung cancer and the resulting slope reflects the effect of cumulative exposure to silica only after adjusting for other confounders (e.g., sex, date of birth, study, etc.). Duration of work or duration of follow-up are other variables (which

are usually much more correlated with age) that could have been used as index variables and the results would not have changed. Age, however, is the recommended index variable by most experts because the increases in lung cancer rates are more related to age than to the duration of work.

27. **First Comment on Page 17:** ( p. 23, lines 30-33. “The individual studies each have limitations. . . . However, the pooled data account for exposure to different forms of crystalline silica at different concentrations and were deemed by the TS as the most appropriate data set for developing the  $^{chronic}ESL_{linear(c)}$ .”) *We question whether the pooled data developed by Steenland et al (2001) really are “appropriate” for calculating a cancer-based chronic ESL for all forms of silica.* The studies considered by Steenland et al. generally did not correct for well-known modeling biases (see Table 1) that can provide non-causal explanations for reported exposure-response associations. To be “appropriate” for regulatory risk assessment, a study should apply appropriate statistical methods (e.g., right column of Table 1) to test, refute, eliminate, or correct for potential biases in the left column. These criteria reflect widely accepted aspects of epidemiological methodology. By these criteria, we believe that the Steenland et al. (2001) study does not provide an “appropriate” data set for developing the  $^{chronic}ESL_{linear(c)}$ .

**TCEQ Response:** The DSD was not revised based on this comment. ACC is commended for an exhaustive table that lists possible biases and recommended statistical methods to correct the biases. ACC’s recommendations should be used in all dose-response modeling of epidemiological data. ACC discredits Steenland et al. results because they “believe” that the epidemiological studies set do not provide an appropriate data set. That is, ACC comments are speculative and have no scientific basis to discredit Steenland et al. (2001) analysis. It is expected and assumed that Steenland et al. (2001), being published in a scientific peer-reviewed journal, was scrutinized by other experts in the field of epidemiological dose-response modeling and accepted their analysis as a scientifically valid analysis. Therefore, Steenland, coauthors, and peer-reviewers very likely based their analysis and reviews on science and not beliefs or conjectures. TCEQ used Steenland et al. (2001) as the basis for the carcinogenic risk assessment because it is the most complete and most scientifically defensible dose-response modeling effort available for silica.

The table with the list of potential biases and recommended methods to correct for the biases is very large, but by no means exhaustive. There are other methods to correct for the biases, there are practicality issues that are important to consider if a dose-response model is to be developed, and there is only marginal benefit of some of the recommended corrections that are not worth considering. For example, a medical doctor recommended exhumation of all deceased workers to ascertain the cause of death and have a uniform diagnose to minimize the impact of possible misdiagnosis/misreporting of the cause of death. Although certainly this is one way to reduce the impact that a few misdiagnosed deaths may have on the dose-response model, the cost is prohibitive (cost in terms of money, effort and time) and the benefit (the impact on the dose response model) is very likely minimal.

28. **Second Comment on Page 17:** *Why does TS use the Steenland et al. (2001) study but not the more recent studies reviewed by Pelucchi et al. (2006)?* Based on their systematic review of epidemiological investigations on silica exposure and lung cancer risk published after the IARC Monograph, including 28 cohort, 15 case-control and two proportionate mortality ratio (PMR) studies,.

**TCEQ Response:** The DSD was not revised based on this comment. TCEQ used Steenland et al. (2001) as the basis for the carcinogenic risk assessment because it is the most complete and most scientifically defensible **dose-response modeling** effort available for silica. Pelucchi et al. (2006), although a very exhaustive and complete study, do not present a dose-response relationship between silica exposure and lung cancer.

29. **Second Comment on Page 17:** Pelucchi et al. (2006) concluded that “The RRs were 1.69 in cohort studies of silicotics only, 1.25 in studies where silicosis status was undefined and 1.19 among non silicotic subjects. ... The RRs were 3.27 in case-control studies of silicotics only, 1.41 in studies where silicosis status was undefined and 0.97 among non silicotic subjects.. (<http://annonc.oxfordjournals.org/cgi/content/full/17/7/1039>)26. In other words, this relatively recent meta-analysis provides support for the hypothesis that exposure to crystalline silica increases lung cancer risk among patients with silicosis, but not necessarily among patients without it. (The interpretation of RRs less than 2 requires careful attention to issues such as those in Table 1 before clear causal interpretations and valid causal inferences can be drawn.)

**TCEQ Response:** The DSD was not revised based on this comment. ACC comments about the RRs and ORs reported in Pelucchi et al., although correct, are misleading. Most often the statistical significance is more important than the magnitude of the RRs and ORs. The comment that “RRs less than 2 requires careful attention to issues such as those in Table 1 before clear causal interpretations and valid causal inferences can be drawn” is unfounded and there are other more important aspects like the number of deaths and the number of person-years on which the RR is based. Thus, an RR of 10 based on just a small number of cases and person-years could be a lot less reliable than an RR of 1.5 based on a large number of cases and a large number of person-years. It is probably because of this misunderstanding about the RRs and ORs that ACC makes the mistake of concluding based on the central estimates of the RRs and ORs without consideration of the significance. For example, the RRs based on the pooled cohort studies included in Pelucchi et al. are:

- 1.69 (95% CI: 1.32-2.16) for silicotic workers (based on 11 studies)
- 1.19 (95% CI: 0.87-1.57) for non-silicotic workers (based on one study)
- 1.25 (95% CI: 1.18-1.33) for studies with undefined silicosis (based on 24 studies)

This indicates that, at the 5% significance level, there was a statistically significant increase in lung cancer for silicotic workers and for workers with undefined silicosis. The studies, however, do not have enough evidence to show the same effect for non-silicotic workers.

The ORs for the case-control studies in Pelucchi et al. are as follows:

- 3.27 (95% CI: 1.32-8.20) for silicotic workers (based on one study)
- 0.97 (95% CI: 0.68-1.38) for non-silicotic workers (based on one study)
- 1.41 (95% CI: 1.18-1.70) for studies with undefined silicosis (based on 13 studies)

This indicates that, at the 5% significance level, there was a statistically significant increase in lung cancer for silicotic workers and for workers with undefined silicosis. The studies, however, do not have enough evidence to show the same effect for non-silicotic workers.

Although ACC indicates that Pelucchi et al. analyses “provides support for the hypothesis that exposure to crystalline silica increases lung cancer risk among patients with silicosis, but not necessarily among patients without it,” Pelucchi et al. use the full distribution of SMRs and ORs to conclude that “the carcinogenic role of silica per se in absence of silicosis is still unclear.”

30. **First Comment on page 20:** (Page 23, lines 40-41. “The authors indirectly validated the quantitative exposure estimates by determining whether or not increasing exposure led to increasing silicosis.) *Exposure estimates are not exposures.* The authors did not determine whether increasing exposure led to increasing silicosis. They only selected exposure estimates that were consistent with this pattern. (Since the cumulative exposure estimates included duration of exposure, it is expected that very long durations/large cumulative exposures will occur disproportionately often for patients with silicosis, even if the estimates of exposure are very inaccurate. Thus, this does not constitute “validation” of the silica-specific component of the exposure estimates.)

**TCEQ Response:** The DSD was not revised based on this comment. ACC is theoretically correct that “exposure estimates are not exposures” and actual exposures are better than estimates of the exposures for dose-response modeling. Practically, however, estimated exposures are the only measures of true exposures available in all epidemiological studies (probably with some minor exceptions, like exposures to radioactive materials, etc.). Estimated exposures are normally unbiased estimates of exposures and, more often than not, serve as excellent surrogates for the exposures. ACC dismisses the relation between silicosis and cumulative exposures by arguing that workers exposed for “very long durations” are expected to develop silicosis, but ACC fails to cite any references that relate duration of exposure and silicosis. ACC fails to recognize that estimated exposures and actual exposures too are surrogates of measures of biologically effective doses that are more relevant for the endpoint but, unfortunately, are usually unknown.

ACC also fails to acknowledge that every time there is an estimate there is some uncertainty and that is why statistical analysis has a role. If everything was deterministic and no variability or errors were present, then there would be no need of statistical analysis.

31. **Second Comment on page 20:** *The Steenland et al. model has not been validated.* The Steenland et al. model has not been used to make testable (potentially falsifiable) predictions that have then been tested and validated using data not used to make the predictions.

**TCEQ Response:** The DSD was not revised based on this comment. Although ACC claims that the Steenland et al. model has not been validated, probably by corresponding with Steenland et al. to ask them that question, there is no indication in the Steenland et al. paper to the contrary. We do agree that model validation, when possible, is an essential part of any results based on dose-response modeling. However, the Steenland et al. paper was peer-reviewed and accepted by expert scientists in the area of dose-response modeling of epidemiological studies and the issue of validity of the model either was not raised by the scientific experts, or they were satisfied with the analyses performed. Steenland et al. applied the same models to ten different and independent epidemiological studies and obtained consistent results; that is, lung cancer mortality increased with increasing cumulative estimates of exposure. Although strictly speaking, consistency of

results is not the same as model validation, the consistency of the results is an indication that the model may have some validity.

32. **Third Comment starting on the bottom of page 20:** *Comment: Steenland et al, used a statistical model that always produces a positive exposure- response relation, no matter what the data show (as long as its input and output variables are positive) – even if the raw data actually show no relation or a negative (protective) relation between exposure and response. Its prediction of a positive relation between silica exposure and lung cancer is therefore meaningless, and does not provide a suitable basis or POD for quantitative risk assessment.*

To see the problem, suppose that we fit a statistical model of the form “ $Y = b * X$ ” to purely random data, formed by sampling X values randomly (uniformly) between 0 and 1 and, independently, sampling Y values randomly (uniformly) between 0 and 1. Then it is easy to see that a least-squares estimate of b will be significantly positive, not because X has any true relation to Y, but because the model goes through (0, 0) and through a scatter plot of data points that are all above and to the right of (0, 0). Sloping upward is all that the regression line can do, given the model “ $Y = b * X$ ”. (This is an example of a bias due solely to model specification error. If the alternative model “ $Y = 0.5 + b * X$ ” were fit to the data instead, then the new least squares estimate of b would be 0.)

**TCEQ Response:** The DSD was not revised based on this comment. ACC has constructed an example and shown that when two positive samples of numbers are randomly and independently generated and a line relating the two samples has to have a non-negative (or positive) slope if the intercept is fixed to be 0. That is true, even if the samples are not independent, even if they are negatively correlated and even if they are not random. It is also true, that if ACC’s example is fit with a linear regression where the intercept is fixed to 1 (i.e.,  $Y=1+b*X$ ) then the slope b is negative (or non-positive). It is also true, that if ACC’s example is fit with a linear regression where the intercept is estimated (i.e.,  $Y=a+b*X$ ) then the slope b is positive approximately 50% of the time and negative approximately 50% of the time.

33. **Comments on page 21:** Steenland et al. have done something similar by fitting the model “ $= \text{Beta} * X$ ” to their data set, where “Y” is ln RR, having almost all positive values (possibly due to biases such as those in Table 1), and X is estimated exposure, consisting entirely of positive values. This model must give a positive estimated value of Beta. But this is only a mathematical necessity, not an empirical finding; it is brought about by the use of a specific mathematical model form that guarantees this result. It does not necessarily tell us anything about the true relation (if any) between exposure and risk. (The linear model ( $RR = 1 + \text{Beta} * X$ ) with positive X values and RR values greater than 1 suffers from a similar bias, of necessarily yielding a positive estimate of Beta)

**TCEQ Response:** The DSD was not revised based on this comment. If ACC comments were true then we agree that Steenland et al. results should be interpreted with caution. However, Steenland, his coauthors and expert scientific peer-reviewers know better. Although the model that ACC claims that Steenland et al. used is incorrect, ACC left out the estimation of the intercept. ACC is partially correct in indicating that if the log-linear model used by Steenland et al. did not include an intercept then the estimates of the slope would have been positive (there are conditions under which this would not be true). However, ACC is incorrect in assuming that there was not an estimate of the intercept. The Cox proportional hazards model does include an estimate of an unspecified

multiplicative background hazard rate (intercept). Thus, the fact that the model for RR (e.g.,  $RR=1+\text{Beta}*X$ ,  $RR=\exp(\text{Beta}*X)$ ) does not explicitly include the intercept, the model fit to the epidemiological dose-response data does include a multiplicative intercept that is not part of RR, but is part of the whole model. That is, the Cox proportional hazards model estimates the hazard rate as the product of a background hazard rate and the RR.

As an illustration, going back to the simple example used by ACC, the model for the linear case ( $Y=a+bX$ ) could be rewritten as  $Y=a(1+s*X)$  and let  $RR=1+sX$ . In this second formulation the RR does not include an intercept (or rather is fixed to 1) but the model for Y does include an intercept.

Sielken & Associates does not believe that this ACC criticism of Steenland et al. dose response modeling is correct. This criticism of ACC to Steenland et al. (2001) (if it can be proven) should be raised in the open literature because it is an important point and, flawed analyses that are published and accepted by expert reviewers, should be brought to the attention of the scientific and regulatory communities.

34. **Comments on bottom of page 21 through Page 22:** Figure 1 plots raw exposure and SMR values from the Steenland et al. paper, without any logarithmic transformations and without using a forced linear fit through the origin to artificially create a positive dose-response relation. Instead, the possibility of a nonlinear fit between  $X =$  median cumulative exposure and  $Y =$  SMR is allowed (by fitting a polynomial instead of a forced straight line). If the true relation were linear through the origin, the model in Figure 1 could show that pattern. But that is not what the data show. Instead, the raw data (exposure estimates and corresponding SMR estimates) *show no positive relation at all between estimated exposure and lung cancer risk*, except possibly (non-significantly) at the highest estimated exposure levels. (See Figure 1 of Steenland et al. for a similar figure based on a spline curve analysis that does not impose the tight mathematical straightjacket used in their main analyses and conclusions. Interestingly, Steenland et al. refer to their spline model as showing a “monotonic increase in risk with increasing exposure,” but the curve in their figure appears to be initially declining.)

**TCEQ Response:** The DSD was not revised based on this comment. Steenland et al. did not indicate that the model fit for the pooled data was obtained from the SMRs of the 10 studies and we do not believe that that was the case. Actually, Steenland et al. clearly indicate on page 776 that “The pooled analyses were conducted via nested case-control analyses using conditional logistic regression (in which the likelihood is equivalent to Cox regression).” then they added “... a risk set for each case was assembled composed of those who had survived to an age at least as great as the case, and which was matched for race (relevant only for US studies), sex, date of birth (within 5 years), and study to the index case.” Could Steenland et al. have done all these matching and analyses using only the data given in Tables 1 and 2? The answer is no. Steenland et al. had to use much more data from each individual study to obtain the coefficients given in their Table 3. In fact, there is no SMR for the South Africa gold study in Table 2 but there are parameter estimates for this same study in Table 3. Thus, the ACC implication that Steenland et al. used the SMRs and median cumulative exposures given in Tables 1 and 2 to estimate the parameters for the pooled analysis is unfounded.

ACC obviously will find different results than what Steenland et al. reported because they are not using the same data nor the same model.

35. **Comments on Page 22:** By selecting different model forms (e.g., logarithmic, exponential, polynomial, linear without intercept, linear with intercept, etc.), a modeler can obtain any regression-based relation he wants – positive, negative, or zero – between exposure and risk from these data. For example, to produce a negative (.protective.) relation between exposure and risk from the data in Figure 1, one could simply fit an exponential model; the best fit is:  $SMR = 1.3414 * \exp(-0.0065 * x)$ . In this model, larger average exposures to silica correspond to reduced risks of lung cancer. Steenland et al, instead chose to fit a logarithmic model with no intercept, and thus obtained a positive rather than a negative relation; in their model, larger estimated exposure values correspond to larger estimated risks of lung cancer. Either model can be fit to the data, and the choice of a model completely determines the resulting statistical relation and conclusions.

**TCEQ Response:** The DSD was not revised based on this comment. As indicated above, ACC is fitting a different model to a different data set and obviously obtaining a different result. Steenland et al. analyses, however, are more complete and more reliable because they are based on the full epidemiological data sets and adjust for covariate effects that cannot be adjusted for using ACC's approach and models. For example, the analyses by Steenland et al. adjust for cohort size, length of follow-up, sex, age, year of birth, calendar year, number of lung cancer deaths, and study. The ACC model fit is based on summary data and does not adjust for any of the possible covariate effects.

Sielken & Associates believes that ACC's criticism of Steenland et al. analyses are inaccurate and cannot be proven with the summary data given in the paper. This criticism of ACC to Steenland et al. (2001), if true, is worthy to be raised by ACC experts in the open literature because it is an important point and, flawed analyses that are published and accepted by expert reviewers, should be brought to the attention of the scientific and regulatory communities.

36. **Comments on Page 22:** Steenland et al. (2001, p. 780) concluded that “We found a positive monotonic exposure-response trend across quintiles of cumulative exposure.” They could equally well have fit a different model (e.g., the above exponential one) and found a negative monotonic exposure-response trend across quintiles of cumulative exposure. This is a good indicator that *the only valid conclusion that can be drawn is that the data set is ambiguous: apart from externally imposed modeling assumptions, it does not show any significant true relation between exposure and risk.* Any interpretation of the Steenland et al. data as supporting a positive (or negative, i.e., protective) causal relation between silica exposure and lung cancer risk is an artifact of modeling choices and preferences, not a valid implication of the data per se.

**TCEQ Response:** The DSD was not revised based on this comment. This is a serious concern that ACC, with the help of their experts, should raise among the scientific community and the regulatory agencies. To date, however, no other scientists have challenged Steenland et al. (2001) analyses and results. In fact, ACC's recommended recent epidemiological study by Pelucchi et al., 2006 cites Steenland et al. and recognize that they “...found and increasing trend in [lung cancer] risk with cumulative exposure.”

37. **Recommendation on bottom of page 22:** *Recommendation* Do not use the study of Steenland et al. (2001) as the key study, since its reported findings and conclusions are driven by unvalidated modeling assumptions, rather than by data.

**TCEQ Response:** The DSD was not revised based on this comment. TCEQ relies on scientific experts that review results before they are published and on scientific arguments that give the opportunity of a response by the authors.

38. **First recommendation on top of page 23:** *Recommendation:* Instead of the study of Steenland et al. (2001), use the larger and more recent studies reviewed by Pelucchi et al. (2006). Analyze the data using nonparametric or flexible statistical models, rather than using a model that imposes pre-determined conclusions on the data.

**TCEQ Response:** The DSD was not revised based on this comment. TCEQ used Steenland et al. (2001) as the basis for the carcinogenic risk assessment because it is the most complete and most scientifically defensible **dose-response modeling** effort available for silica. Pelucchi et al. (2006), although a very exhaustive and complete study, do not present a dose-response relationship (neither positive or negative) between silica exposure and lung cancer. In addition, Pelucchi et al., 2006 cites Steenland et al. and recognize that they "...found an increasing trend in [lung cancer] risk with cumulative exposure." Pelucchi et al. 2006 accepts Steenland et al. findings and does not perform any alternative dose-response model.

39. **Second recommendation on top of page 23:** *Recommendation:* Recognize that the best current evidence is that silica exposure increases lung cancer risk only if there is sufficient exposure to cause silicosis.

**TCEQ Response:** The DSD was not revised based on this comment. As discussed above in several occasions and as indicated by Checkoway et al. (1999), Pelucchi et al. (2006) and Erren et al. (2008), the "carcinogenic role of silica per se in absence of silicosis **is still unclear**" (emphasis added)

40. **First Comment on Page 23:** (p. 24, lines 11-12. "The authors indicate that lung cancer was consistently related to silica exposure across all studies.") *There is no such consistent relation.*

**TCEQ Response:** The DSD was not revised based on this comment. The comments ACC makes here are a repeat of comments made previously and have already been addressed.

41. **Second Comment on Page 23:** (Page 24, lines 12-14. "A log-linear multiplicative risk model was selected as the preferred model. The basis of this selection included the historical use of this model for human epidemiological data and the lack of a biological basis for selecting an alternative model.") *The selected model is not appropriate for lung cancer.*

**TCEQ Response:** The DSD was not revised based on this comment. The scientific community agrees that parsimonious models (e.g., linear or log-linear multiplicative relative risk models) are to be preferred over other less-plausible models. If there is biological information that allows for a biologically-based model, then that model would be preferable. ACC's suggestion of using a biologically-based model is the best scientific recommendation that can be given in general. However, the scientific mechanism and scientific biological information of how silica causes lung cancer have not been conclusively determined.

42. **Comment on Page 24:** (Page 24, line 17. “The cumulative exposure metric fit the data well and was used in this assessment.) *The cumulative exposure metric does not fit the data well. . .*

**TCEQ Response:** The DSD has been revised based on this comment. The sentence “The cumulative exposure metric fit the data well and was used in this assessment.” has been changed to “The cumulative exposure metric was used in this assessment because it fits the data better than the model with the average exposure metric.”

43. **Recommendation on Page 24:** *Recommendation:* Use statistical models and methods that explicitly model measurement and estimation errors for exposure intensities and durations, and that keep duration and intensity as separate explanatory variables. Use dosimetric models that allow different exposure intensities to have different potencies and that recognize that a high average exposure intensity may also be associated with relatively high peak exposures that could disproportionately contribute to risk. (Kriebel D, Checkoway H, Pearce N. Exposure and dose modelling in occupational epidemiology. *Occup Environ Med.* 2007 Jul;64(7):492-8.)

**TCEQ Response:** The DSD was not revised based on this comment. ACC’s recommendation may or may not have been followed by Steenland et al. The decision of Steenland et al. of using estimated cumulative exposure as the dose metric, however, seems consistent with the recommendation of ACC of using the Kriebel et al. (2007) as a guide for selection of dose metric. Kriebel et al. (2007) state “Cumulative exposure, the time integral of exposure intensity (equation 2), is a commonly used summary measure in occupational epidemiology. There are good reasons for this. First, taking the example of an inhaled dust with the lung as the target organ, cumulative exposure will be proportional to dose in the target organ if one assumes that ventilation rates are constant over time and similar among members of the cohort, and that the fraction of the inhaled particles deposited is also roughly constant over time and among subjects. Second, target organ dose is often assumed to be directly proportional to biological damage and disease risk. This appears to be a valid assumption for a wide variety of disease mechanisms, although we will discuss some exceptions later. Third, cumulative exposure has been shown to correlate strongly with disease risk in a wide variety of exposure–response associations.” Furthermore, in Table 1 of Kriebel et al., they list cumulative exposure as a common summary measure of exposure for the irreversible physiological process of silica. Checkoway et al. (1999) (Checkoway is coauthor with Kriebel et al. in the paper recommended by ACC) used estimated cumulative exposure for dose-response modeling of silica and lung cancer (Checkoway, H., Hughes J.M., Weill, H., Seixas, N.S., and Demers, P.A. 1999. Crystalline silica exposure, radiological silicosis, and lung cancer mortality in diatomaceous earth industry workers. *Thorax*, 54:56-59.) In conclusion, Steenland et al. did follow what the experts in dose metrics recommend and, more importantly, Steenland et al. used a dose metric that the experts (e.g., Checkoway et al.) in dose metrics would have used for the exact same substance and endpoint (i.e., silica and lung cancer).

Similar to Steenland et al., neither Kriebel et al. (2007) and Checkoway et al. (1999) explicitly indicate whether they did anything about exposure estimation errors and did not address how to resolve the discrepancies between estimated and actual exposures.

**APPENDIX A**

**The Association of Electric Companies of Texas (“AECT”)  
Comments Regarding the  
TCEQ Silica Development Support Document**



Charles Patton  
Chair

Vicki Oswalt  
Vice Chair

John W. Fainter, Jr.  
President & CEO

Walton L. Baum, III  
Executive Vice President

Russell C. Mullins  
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Member Companies

AEP SWEPSCO

AEP Texas

CenterPoint Energy

Direct Energy

El Paso Electric Company

Entergy Texas

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Luminant

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January 5, 2009

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

Re: The Association of Electric Companies of Texas' comments to proposed Development Support Document ("DSD") and revised effects screening levels ("ESLs") for silica

Dear Toxicology Section:

The Association of Electric Companies of Texas ("AECT") appreciates the opportunity to submit these comments regarding the proposed Development Support Document ("DSD") and revised effects screening levels ("ESLs") for silica.

AECT is a trade association representing electric companies in Texas. Organized in 1978, AECT provides a forum for member companies' representatives to exchange information on their industry, and to communicate with state and federal governmental officials.

AECT appreciates that the TCEQ Toxicology Section followed a methodical, scientific process in developing the proposed DSD and revised ESLs for silica, which process included requesting that Toxicology Excellence for Risk Assessment ("TERA") conduct what the TCEQ refers to as a "scientific technical evaluation" of the April, 2008 proposed DSD and revised ESLs for silica. AECT believes that such process has resulted in proposed revised silica ESLs that are more scientifically supportable and appropriate than the current ESLs.


AECT recognizes that like for the ESLs for other compounds, TCEQ is proposing to establish the silica ESLs at concentrations that are lower than concentrations that may produce any adverse health effects, such that the silica ESLs will be protective of the general public, including sensitive subgroups such as children, the elderly, or people with existing respiratory conditions, with a margin of safety. As a result, if the ambient concentration of silica were to exceed any of the silica ESLs, that would not mean that any adverse health effect would occur, but rather that further evaluation would be warranted.

Margie McAllister  
September 2, 2008  
Page 2

Based on the foregoing, AECT supports the proposed revised silica ESLs and DSD.

Thank you for your consideration of these comments. If you should have any questions, please contact Keith Courtney at (512) 370-2813.

Sincerely,



John W. Fainter  
AECT President & CEO

**APPENDIX B**

**North American Insulation Manufacturers Association (“NAIMA”)  
Comments Regarding the TCEQ  
Silica Development Support Document**

BEFORE THE  
TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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In Re:

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY'S DEVELOPMENT SUPPORT  
DOCUMENT ON SILICA (Proposed September 2008).

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COMMENTS OF THE  
NORTH AMERICAN INSULATION  
MANUFACTURERS ASSOCIATION

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January 30, 2009

**COMMENTS OF THE NORTH AMERICAN  
INSULATION MANUFACTURERS ASSOCIATION  
ON THE TEXAS COMMISSION ON ENVIRONMENTAL QUALITY'S  
DEVELOPMENT SUPPORT DOCUMENT ON SILICA  
(PROPOSED SEPTEMBER 2008)**

## INTRODUCTION

The North American Insulation Manufacturers Association (“NAIMA”) appreciates the opportunity to submit comments on the Texas Commission on Environmental Quality’s (“TCEQ”) proposed Development Support Document on Silica. NAIMA is the association for North American manufacturers of fiber glass and rock and slag wool insulation products. NAIMA promotes energy efficiency and environmental preservation through the use of fiber glass insulation and encourages the safe production and use of these materials. Because fiber glass insulation is a glass (silica-based) product and because there are three fiber glass insulation manufacturing plants in the state of Texas,<sup>1</sup> NAIMA has a keen interest in assisting the TCEQ in revising the Development Support Document on Silica to be accurate, scientifically sound, and reflective of the established scientific and regulatory distinctions between crystalline and amorphous types of silica.

## BACKGROUND ON FIBER GLASS INSULATION

Fiber glass insulation is a glass (silica-based) product. To be more precise, fiber glass insulation is a man-made vitreous fiber (“MMVF”), a generic name used to describe an inorganic fibrous material manufactured primarily from glass, rock, mineral, slag and processed inorganic oxides. MMVFs are non-crystalline (glassy, vitreous, amorphous). Virtually all MMVFs are non-crystalline silica based and contain various amounts of other inorganic oxides. The non-silica components typically include, but are not limited to, oxides of alkaline earths, alkalis, aluminum, boron, iron and zirconium. Depending on the process of fiber formation, MMVFs are produced either as wool, which is a mass of tangled, discontinuous fibers of variable lengths and diameters, or as filaments, which are continuous fibers with diameters having ranges that are more uniform and typically thicker than those of wool. Therefore, a distinction between crystalline and amorphous silica in the TCEQ’s Development Support Document is particularly important for glass industries, including fiber glass insulation manufacturing. As a result, those manufacturing entities producing glass products in the State of Texas, where sand is a major raw ingredient, will be significantly impacted if TCEQ does not fully acknowledge that distinction and modify any regulatory proposal to reflect such a distinction.

As discussed more fully below, insulation wools are vital tools for increasing the energy efficiency of buildings. That increase in energy efficiency plays a significant role in reducing pollutants such as greenhouse gases that are associated with climate change.

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<sup>1</sup> CertainTeed Corporation, Sherman, Texas; Johns Manville, Cleburne, Texas; and Owens Corning, Waxahachie, Texas.

## THE TCEQ DEVELOPMENT SUPPORT DOCUMENT SHOULD RECOGNIZE THE DIFFERENCE BETWEEN CRYSTALLINE AND AMORPHOUS SILICA

The current Development Support Document on Silica acknowledges that other agencies treat crystalline and amorphous silica differently. Despite these regulatory distinctions, the TCEQ document makes a contrary “policy decision” to treat all forms of silica alike, and in so doing, references a single citation that sixty percent of natural amorphous silica is crystalline silica and cites an American Conference of Governmental Industrial Hygienists (“ACGIH”) annual study of amorphous silica, which actually shows TCEQ’s “policy” determination to be wholly unscientific. With this reference, the TCEQ seems to suggest that no further distinction is merited. Yet a distinction is necessary because of the disparity and confusion such a departure will cause in the regulated community. Importantly, treating the two types of silica the same is not, as TCEQ states, “conservative” in the real world. If regulators do not recognize sharply different hazard and risk potentials, they discourage the regulated community from using less hazardous materials, undermine warnings, and impose costs that have virtually no health benefits.

To illustrate, the draft does not fully discuss all of the classifications and regulations of silica currently in place which consistently distinguish between crystalline and amorphous silica. For example, the International Agency for Research on Cancer (“IARC”) 1997 Monograph on “Silica, Some Silicates,” and other materials, noted that in glass manufacturing, the “airborne dust from the mixed batch commonly used contains only 1-5% crystalline silica.” *Id.* at 77. Because sand and dusts are commonly generated in many industries, including agriculture and construction, focusing control on the crystalline and similar types of silica that have shown demonstrated toxicity, should have priority from a public health perspective.

Treating amorphous silica in the same way undermines public health protections given limited resources that are available in the real world. The IARC 1997 Monograph also has a concise discussion of the chemical and physical properties that differentiate the various forms of silica. *Id.* at 41-52. This discussion is an important predicate for the decision by IARC to classify crystalline silica forms of silica very differently than amorphous forms.

Further, the National Institute for Occupational Safety and Health (“NIOSH”) recommends an exposure limit of 0.05 mg/m<sup>3</sup> for crystalline silica and 6 mg/m<sup>3</sup> for amorphous silica – a 1200 fold difference.<sup>2</sup> The current permissible exposure limit (“PEL”) (8-hour TWA) set by the U.S. Occupational Safety and Health Administration (“OSHA”) for crystalline silica (as respirable quartz) is 10 mg/m<sup>3</sup> divided by the value “%SiO<sub>2</sub> + 2,” whereas the PEL (8-hour TWA) for amorphous silica is 80 mg/m<sup>3</sup> divided by the value “%SiO<sub>2</sub>.”<sup>3</sup> ACGIH has set a threshold limit value of 0.025 mg/m<sup>3</sup> for crystalline silica and has not set a limit for amorphous. Plainly ACGIH recognizes a difference.

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<sup>2</sup> NIOSH Pocket Guide to Chemical Hazards (Sept. 2005) (available at <http://www.dcd.gov/niosh/npg/npgd0553.html>) (crystalline silica); <http://www.cdc.gov/niosh/npt/npgd0552.html> (amorphous silica)).

<sup>3</sup> 29 CFR § 1910.1000, Table Z-3. OSHA has placed the regulation of crystalline silica on its regulatory agenda. Department of Labor, Regulatory Plan, OSHA, 69 Fed. Reg. 72781 (December 13, 2004). The absence of amorphous silica from OSHA’s plan further illustrates the Administration’s distinction between crystalline silica and amorphous silica.

As further support for distinguishing crystalline and amorphous silicas, TCEQ should note that U.S. OSHA is in the process of a Section 6(b) Occupational Health Standard for “crystalline silica.” OSHA published earlier this month its peer review plan for its risk assessment of silica entitled “Health Effects Analysis and Quantitative Risk Assessment for Crystalline Silica.”<sup>4</sup> This peer review is scheduled for completion next month – February 2009. While NAIMA recognizes that TCEQ’s responsibilities are different from, and broader than, those of OSHA, the fact that OSHA is working on a new standard that only covers crystalline silica is yet another indication that amorphous silica should not be lumped together with the crystalline forms of silica, and should be treated differently for hazard and risk purposes.

Similarly, the California Office of Environmental Health Hazard Assessment (“OEHHA”) established in 2005 a chronic Reference Exposure Level (“REL”) that, contrary to the TCEQ proposal, covers only “SILICA (CRYSTALLINE, RESPIRABLE) (silicon dioxide, quartz, tridymite, cristobalite) CAS Registry Number: 7631-86-9.”<sup>5</sup> Since OEHHA’s REL specifically covers airborne, non-occupational exposures, it should be particularly persuasive to TCEQ that amorphous silica should not be treated the same as crystalline silica. To do so places Texas at a severe competitive disadvantage as a location for manufacturing and other job-producing activities.

In 2002, the U.S. EPA, in granting a petition to exempt amorphous silica from the requirements of a pesticide inert ingredient tolerance, summarized the toxicity data concisely and persuasively as follows:

Silica, amorphous, fumed (crystalline free) has a demonstrated lack of toxicity. The acute toxicity studies are toxicity category IV. The mutagenicity studies are negative. Silica, amorphous, fumed (crystalline free) is not classifiable, as to carcinogenicity however, given its amorphous nature, it is not expected to pose a carcinogenic risk. Silicas are considered to be inert when ingested, and due to the high molecular weight it is unlikely to be absorbed through the skin. There should be no concerns for human health, whether the exposure is acute, subchronic, or chronic by any route. Thus, based on the very low toxicity of silica, amorphous, fumed (crystalline free), the Agency has determined that there is a reasonable certainty of no harm to the U.S. population, including infants and children, from aggregate exposure to residues of silica, amorphous, fumed (crystalline free) and that a tolerance is not necessary. 67 Fed. Reg. 3416 (May 15, 2002).

Because many precedents for distinguishing crystalline silica from amorphous forms have been firmly established, a departure that either blurs or confuses that distinction will send mixed and unscientific signals in the regulated community. Moreover, the TCEQ has not articulated a basis or scientific justification for departing from so many solid precedents. Most of the agencies that made these decisions did so on a much stronger scientific analysis than that undertaken by TCEQ. Therefore, NAIMA urges the TCEQ to acknowledge this distinction to avoid possible

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<sup>4</sup> [http://www.osha.gov/dsg/peer\\_review/peer\\_agenda.html](http://www.osha.gov/dsg/peer_review/peer_agenda.html).

<sup>5</sup> [http://oehha.ca.gov/air/chronic\\_rels/silica\\_final.html](http://oehha.ca.gov/air/chronic_rels/silica_final.html).

regulation of amorphous silica under the same standard established for crystalline silica. For now, the proposal should be limited to crystalline forms of silica. A separate document, or a vastly different draft, should be prepared.

## THE FIBER GLASS INSULATION INDUSTRY PROVIDES NUMEROUS BENEFITS TO TEXAS BUSINESSES AND CITIZENS

As noted above, current fiber glass insulation plants operating in Texas use amorphous silica to produce its fiber glass insulation products. As with all elements of the fiber glass manufacturing process, exposures to silica are strictly controlled and monitored. Obviously, fiber glass manufacturers are concerned about the possible impact upon its manufacturing operations if a different and disparate standard for silica were to be created for its Texas operations. For the benefits derived from uniformity and predictability, NAIMA again urges the TCEQ to recognize the differences between amorphous silica and crystalline silica in the Development Support Document to avoid onerous and burdensome regulation of silica that is not found in any other jurisdiction. NAIMA does not hesitate to urge such action because it is supported by the weight of scientific evidence by virtually all regulatory authorities. Moreover, fiber glass insulation provides numerous benefits to the citizens of Texas that merit protection and encouragement from the State.

### *Insulation Delivers Energy Savings and Pollution Reduction*

Fiber glass insulation delivers energy savings through increased energy efficiency. In fact, the State of Texas can achieve many of its pollution reduction goals through energy savings and increased energy efficiency. Indeed, President Obama has recognized the importance of insulation by making weatherization improvements a key part of the proposed Economic Stimulus Bill, which passed the House of Representatives on January 28, 2009. This recognition of the importance of insulation as a key energy efficiency tool in the Economic Stimulus Bill is based on a series of studies, some of which are summarized below.

#### Energy Savings

The U.S. EPA has recognized that “energy efficiency has significant advantages because, as a strategy for reducing GHG emissions, . . . increasing energy efficiency and conservation . . . [is] available today.” (73 Fed. Reg. at 44,404). In other words, energy efficiency is an existing technology that is immediately available. Moreover, it has minimal financial barriers as it is the most cost-effective solution to GHGs available.<sup>6</sup> EPA also recognizes the energy savings and pollution reduction that may be achieved through the increased energy efficiency of buildings.

EPA has also concluded that improving energy efficiency in buildings could “substantially reduce emissions between now and 2030.” (73 Fed. Reg. at 44,405). EPA’s conclusions are certainly consistent with other findings that buildings are the largest users of energy and the largest U.S. source of anthropogenic GHGs.

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<sup>6</sup> Enkvist, Per-Anders, Tomas Nauclicr and Jerker Rosander. 2007. “A Cost Curve for Greenhouse Gas Reduction.” *The McKinsey Quarterly* 1: 38.

In recent testimony before the Subcommittee on Energy and Air Quality of the Committee on Energy and Commerce of the U.S. House of Representatives, William Fay, Executive Director of the Energy Efficient Codes Coalition, stated that “homes and commercial buildings are this nation’s largest sector of energy use and – because of the close relationship between greenhouse gases and energy consumption – also the largest US source of anthropogenic greenhouse gases. Suffice it to say that buildings – and particularly residences – represent one of the last great frontiers of wasted energy.”<sup>7</sup>

According to the U.S. Department of Energy (“DOE”), 40 percent of U.S. energy is consumed by buildings.<sup>8</sup> Some data from the U.S. Energy Information Administration (“EIA”) estimates that buildings are responsible for almost half (48 percent) of all GHG emissions. The EIA reports that 76 percent of all electricity generated by U.S. power plants goes to supply the buildings sector.<sup>9</sup> In fact, the World Business Council for Sustainable Energy (“WBCSE”) states those buildings are responsible for at least 40 percent of energy use worldwide, especially in countries such as China and India.<sup>10</sup>

The Whole Building Design Guide project states that “buildings in the United States consume 39% of America’s energy and 68% of its electricity. Furthermore, buildings generate 38% of the carbon dioxide (the primary greenhouse gas associated with climate change), 49% of the sulfur dioxide, and 25% of the nitrogen oxides found in the air.”<sup>11</sup>

Insulation is a key resource for improving energy efficiency in buildings and achieving the accompanying reduction in greenhouse gases.

In “A Cost Curve for Greenhouse Gas Reduction,” the *McKinsey Quarterly* reports “that almost a quarter of possible emission reductions would result from measures (such as better insulation in buildings) that carry no net life cycle cost” – in effect they come free of charge.<sup>12</sup> As the graphic from the above-referenced article demonstrates, no other efficiency measure is as cost effective as building insulation.

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<sup>7</sup> Energy Efficient Codes Coalition, Testimony of William D. Fay Before the Subcommittee on Energy and Air Quality of the Committee on Energy and Commerce, U.S. House of Representatives, Thursday, July 17, 2008.

<sup>8</sup> *2007 Building Energy Data Book*, U.S. Department of Energy, Office of Planning, Budget and Analysis, Energy Efficiency and Renewable Energy, Prepared by D&R International Ltd., September 2007.

<sup>9</sup> 2030, Inc. / Architecture 2030, “Global Warming, Climate Change, and Built Environment,” 2008 (available at <http://www.architecture2030.org/>).

<sup>10</sup> “Slashing buildings energy use: Why not?” (available at <http://www.wbcd.org/plugins/DocSearch/details.asp?type=DocDet&ObjectId=Mjk1NzM>).

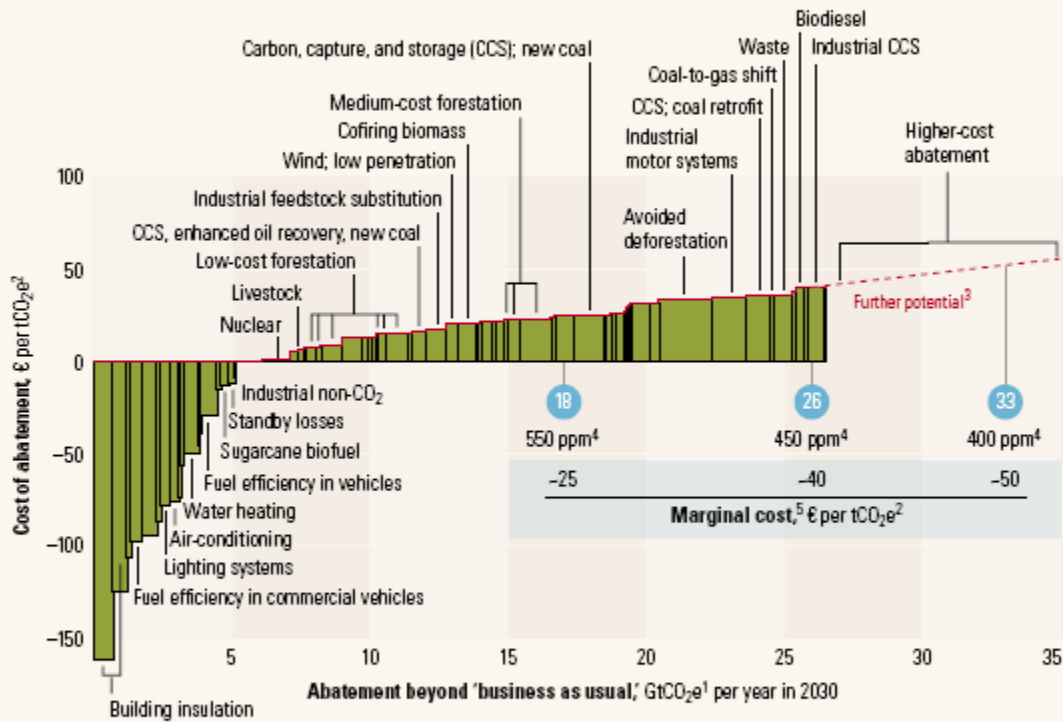
<sup>11</sup> WBDG Sustainable Committee, “Optimize Energy Use,” (available at [http://www.wbdg.org/design/minimize\\_consumption.php](http://www.wbdg.org/design/minimize_consumption.php)).

<sup>12</sup> Enkvist, Per-Anders, Tomas Nauc ler and Jerker Rosander. 2007. “A Cost Curve for Greenhouse Gas Reduction.” *The McKinsey Quarterly* 1: 38.

## What might it cost?

Global cost curve for greenhouse-gas abatement measures beyond 'business as usual'; greenhouse gases measured in GtCO<sub>2</sub>e<sup>1</sup>

● Approximate abatement required beyond 'business as usual,' 2030



<sup>1</sup>GtCO<sub>2</sub>e – gigaton of carbon dioxide equivalent; “business as usual” based on emissions growth driven mainly by increasing demand for energy and transport around the world and by tropical deforestation.

<sup>2</sup>tCO<sub>2</sub>e – ton of carbon dioxide equivalent.

<sup>3</sup>Measures costing more than €40 a ton were not the focus of this study.

<sup>4</sup>Atmospheric concentration of all greenhouse gases recalculated into CO<sub>2</sub> equivalents; ppm – parts per million.

<sup>5</sup>Marginal cost of avoiding emissions of 1 ton of CO<sub>2</sub> equivalents in each abatement demand scenario.

Not only is insulation cost effective, it is practical, too. Insulation is easily installed and the materials are readily available.

## Pollution Reduction

Two studies conducted by the Harvard School of Public Health (the “Harvard Studies”) analyzed the benefits of increased insulation and projected resultant reductions of the following pollutants: PM<sub>2.5</sub>, NO<sub>x</sub>, and SO<sub>2</sub>. Data were developed by a model designed to predict emissions reductions of fine particulate matter and its precursors, nitrogen dioxide, and sulfur dioxide.

While the pollutants analyzed in the Harvard Studies are not technically listed as one of the six Kyoto Protocol greenhouse gases, some of these pollutants are deemed as indirect greenhouse gases or other greenhouse gases.<sup>13</sup> For example, another pathway for NO<sub>x</sub> in the atmosphere is

<sup>13</sup> GreenHouse Gas Online.org, “Other Indirect Greenhouse Gases – NO<sub>x</sub>” (available at <http://www.ghgonline.org/othernox.htm>) [hereinafter GHG Online]; Science Daily, “Sulfur Dioxide May Have

that of dry deposition back on land. Such deposition can lead to increased emissions of the direct greenhouse gas nitrous oxide (N<sub>2</sub>O).<sup>14</sup>

The first Harvard Study found that nearly 65 percent of U.S. homes (46 million) have insulation levels that are inadequate by even 2000 energy standards. Likely, that is equally true of commercial and industrial buildings.<sup>15</sup> If just these homes were insulated to levels equivalent to the 2003 IECC (with 2004 IECC Supplement), more than 800 trillion Btus – 76 supertankers of crude oil or 800 billion cubic feet of natural gas – could be saved each year. Savings would be similarly dramatic if commercial and industrial buildings upgraded their current insulation levels.

As reported by the Harvard School of Public Health, bringing all existing homes up to 2003 IECC (with 2004 IECC Supplement) codes would result in a significant reduction of pollutants:

According to our calibrated energy model, increasing residential insulation in the 46 million existing homes where insulation retrofits are necessary would save approximately 800 TBTU per year – 17 MMBTU . . . per household per year. . . . Given these energy savings, the aggregate emission reductions from residential fuel combustion and power plants include approximately 31,000 fewer tons per year of PM<sub>2.5</sub>, 100,000 fewer tons per year of NO<sub>x</sub>, and 190,000 fewer ton per year of SO<sub>2</sub>.<sup>16</sup>

The Harvard study is careful to point out that the majority of emissions are linked to power plants and that a significant share of pollution reduction achieved from increased insulation would be from power plants:

For all three pollutants, the majority of emissions are linked to power plants (69% for PM<sub>2.5</sub>, 76% for NO<sub>x</sub>, and 89% for SO<sub>2</sub>), even though only 39% of energy savings is related to electricity generation. . . .<sup>17</sup>

This is consistent with EPA's identification of power plants as a significant source of SO<sub>2</sub>.<sup>18</sup>

According to the second Harvard Study, each year, more than 1.2 million new homes are built in the U.S.<sup>19</sup> Moreover, this Study shows that by insulating these homes to even the modest 2000

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Helped Maintain A Warm Early Mars" (Dec. 30, 2007) (available at <http://www.sciencedaily.com/releases/2007/12/071220140813.htm>).

<sup>14</sup> GHG Online.

<sup>15</sup> A study conducted by the Alliance to Save Energy reported that insulation in existing commercial buildings saves at least 30 percent of the total U.S. commercial consumption – 2,305 trillion Btus. The study found that if all existing commercial buildings had been built to ASHRAE 90.1 standards, an additional 380 trillion Btus would have been saved. Moreover, the report stated that 20 percent of commercial buildings have no insulation and, if retrofitted, could save a potential 497 trillion Btus. The report also found that if all existing commercial buildings had been insulated to ASHRAE 90.1 standards, carbon emissions would have been 10.5 million short tons lower. Alliance to Save Energy, *Green and Clean: The Economic, Energy, and Environmental Benefits of Insulation* (Washington, DC: April 2001, pp. 12-16. The study also found dramatic energy savings for manufacturing facilities with accompanying reductions in pollution. *Ibid.* at pp. 18-23.

<sup>16</sup> Levy, Nishioka and Spengler at p. 7.

<sup>17</sup> *Ibid.*

<sup>18</sup> 70 Fed. Reg. at 65,994.

IECC levels would save 300 billion Btus over ten years – 28 supertankers of crude oil or 300 billion cubic feet of natural gas. Based on the magnitude of these energy savings, Harvard researchers estimate the following reduction of pollutants:

First focusing on the aggregate emission reductions, the 300 TBTU energy savings is associated with reduced emissions of approximately 1,000 tons of PM<sub>2.5</sub>, 40,000 tons of SO<sub>2</sub>, and 30,000 tons of NO<sub>x</sub> during the 10-year period. . . . On a per-unit basis, the emission reductions [for] PM<sub>2.5</sub> are fairly similar across regions (ranging between 0.02 kg/year in the Midwest and 0.01 kg/year in other regions). Patterns are similar for NO<sub>x</sub> with the South and Midwest having the greatest per-unit emission reductions. At the state level, Texas had the greatest reduction of PM<sub>2.5</sub>, and Virginia had the greatest reductions of NO<sub>x</sub> and SO<sub>2</sub>, all of which were largely related to substantial electric space heating.<sup>20</sup>

Significant reductions can and will be achieved throughout the United States with improved energy efficiency, including increased insulation.

*Economic Benefits Derived from the Fiber Glass and Rock and Slag Wool Insulation Industry*

The fiber glass and rock and slag wool insulation industry directly employs well over 16,000<sup>21</sup> workers in 41 North American plants in high-paying manufacturing jobs at a time when U.S. businesses and consumers have increasingly turned to many foreign manufactured products. Fiber glass and rock and slag wool insulation products provide tens of thousands of other good jobs for fabricators and installers.<sup>22</sup> The Occupational Safety and Health Administration (“OSHA”) estimated that over 225,000 workers in the United States are employed in fiber glass or mineral wool insulation production and installation.<sup>23</sup> Therefore, NAIMA’s members provide valuable manufacturing jobs to American workers at a time when many industries are moving operations and jobs overseas. Specifically, as noted above, Texas has three fiber glass manufacturing plants and one slag wool manufacturing plant, which is located in Nolanville.

A domestic fiber glass and rock and slag wool insulation industry helps maintain a viable economy in North America. The fiber glass and rock and slag wool insulation industry produces products for the American market; employs directly or indirectly over 225,000 workers; provides domestic workers with high-paying, skilled employment; and provides significant employee

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<sup>19</sup> Given the current slump in the housing market, this number would not reflect current building patterns.

<sup>20</sup> Yurika Nishioka, Jonathan I. Levy, Gregory A. Norris, Andrew Wilson, Patrick Hofstetter, and John D. Spengler, “Integrating Risk Assessment and Life Cycle Assessment: A Case Study of Insulation,” *Risk Analysis*, Vol. 22, No. 5, 2002, p. 1009.

<sup>21</sup> The U.S. mineral wool manufacturing industry “comprises establishments primarily engaged in manufacturing mineral wool and mineral wool (i.e., fiberglass) insulation products made of such siliceous materials as rock, slag, and glass or combinations thereof.” (See U.S. Census Bureau, 2002 Economic Census: Mineral Wool Manufacturing, Appendix B (Jan. 2005) (Ex. 46-64).) OSHA estimates that fiber glass insulation workers comprise at least 80 percent, or more than 12,000, of the mineral wool manufacturing industry’s 15,788 production workers. (See *Ibid.* at p. 1.)

<sup>22</sup> OSHA, OSHA Priority Planning Process: Announcement of the Results of the OSHA Priority Planning Process 58 (Dec. 13, 1995).

<sup>23</sup> *Ibid.*

benefits.<sup>24</sup> The North American fiber glass and rock and slag wool insulation industry continues to benefit both its domestic workers and customers because internationally traded goods have become an increasingly large share of the American market.

The sum of U.S. exports and imported manufactured goods, as a percentage of U.S. domestic production of manufactured goods, has doubled since 1987 from 20 percent to 40 percent.<sup>25</sup> Despite this trend, the U.S. fiber glass and rock and slag wool insulation industry has been able to supply virtually all of the needs of the domestic building industry for residential, commercial, and industrial insulation products without turning to either imported insulation products or offshore production. Many U.S. manufacturers in other industries have shut down or moved production overseas to other countries, but fiber glass and rock and slag wool insulation manufacturers have remained in the United States and preserved many high-paying manufacturing jobs.<sup>26</sup>

### Recycled Content

Using recycled materials in the manufacturing of insulation reduces the depletion of natural resources. Today's fiber glass insulation contains upward of 40 percent recycled glass, depending upon the manufacturer and the specific facility. Fiber glass insulation is the second largest user of glass cullet.<sup>27</sup> Slag wool insulation contains approximately 70 percent recycled blast furnace slag and rock wool insulation contains 10-15 percent recycled blast furnace slag.

NAIMA tracks the use of pre-and post-consumer recycled materials in its members' insulation products. The most recent survey showed that in 2006 and 2007, NAIMA member companies in the U.S. and Canada used almost 5 billion pounds of recycled glass and blast furnace slag in the production of residential, commercial, industrial and air handling thermal and acoustical insulation.

More specifically, the data showed that facilities in the U.S. used more than 2.9 billion pounds of recycled glass and nearly 1.3 billion pounds of slag in 2006 and 2007. This represented an increase in recycled glass use of 107 percent and in reclaimed slag use of 55.6 percent over 2005. Use of recycled glass by NAIMA members has almost tripled since NAIMA first surveyed its members in 1992.

### CONCLUSION

NAIMA urges TCEQ to focus its proposal on the crystalline forms of silica. This approach would recognize the well-established human health hazard differences between the crystalline and amorphous forms. Regulating only the crystalline forms would be consistent with the scientific data and with the regulatory and hazard classification approaches used by virtually all

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<sup>24</sup> U.S. Census Bureau, 2002 Economic Census: Mineral Wool Manufacturing at 5.

<sup>25</sup> Joel Popkin and Company, Securing America's Future: The Case for a Strong Manufacturing Base 9 (June 2003).

<sup>26</sup> *Ibid.*

<sup>27</sup> California Integrated Waste Management Board, *Market Status Report, Container & Plate Glass*, [ciwmb.ca.gov/markets/StatusReport.Glass.html](http://ciwmb.ca.gov/markets/StatusReport.Glass.html); Chaz Miller, *Glass Containers*, [Wasteage.com/Recycling\\_And\\_Processing/Andwaste\\_glass\\_containers\\_4/](http://Wasteage.com/Recycling_And_Processing/Andwaste_glass_containers_4/).

other agencies (International, Federal, and State). Recognizing these differences would avoid confusion in the regulated community and direct efforts toward controlling and avoiding exposures that really matter to human health.

Otherwise, for TCEQ to sweep all sand, one of the most ubiquitous minerals on the earth, into the same health hazard bucket will promote over-regulation, encourage unnecessary public concern and waste limited resources. The currently proposed approach would thus fail to protect the citizens of Texas from the exposures that truly matter in the real world. A properly focused approach consistent with the scientific data would also permit allocation of State enforcement resources more efficiently. Texas should not be the only jurisdiction to fail to make this important, scientifically sound distinction among the various forms of silica.

In addition, NAIMA believes that the significant energy efficiency benefits derived from fiber glass insulation, reduction of greenhouse gas emissions and use of recycled glass, merit consideration and protection by TCEQ. Moreover, fiber glass insulation manufacturers provide important employment in the State of Texas and TCEQ should also give those benefits consideration. In these challenging economic times, Texas should do all it can to encourage employment in the manufacturing sector and not adopt an approach to silica that will make manufacturing in Texas economically and technologically uncompetitive.

**APPENDIX C**

**American Chemistry Council's Crystalline Silica Panel ("ACC")  
Comments Regarding the  
TCEQ Silica Development Support Document**



January 30, 2009

Toxicology Section, MC 168  
Texas Commission on Environmental Quality  
12100 Park 35 Circle, Bldg. F  
Austin, TX 78753

**Re: Proposed Silica Development Support Document (September 2008)**

Dear Sir/Madam:

The American Chemistry Council's Crystalline Silica Panel ("Panel"), is pleased to submit comments on the Texas Commission on Environmental Quality's (TCEQ) Proposed Silica Development Support Document (DSD).<sup>1</sup> The Comments were prepared by Dr. Louis Anthony Cox, Jr. (Curriculum Vitae is attached) at the request of the Panel.

As set forth in the accompanying comments, the Panel believes that the DSD is fraught with scientifically questionable statements, assumptions, positions, and quantitative assessments. Moreover, the DSD utilizes biased or otherwise inappropriate models that are not reflective of current scientific understanding of silica. In particular,

- In the DSD, the TCEQ treats all forms of silica as presenting silicosis and lung cancer hazards (and, on that basis, proceeds to conduct quantitative risk assessments) without presenting evidence to demonstrate that this hazard identification assumption is correct and without even thoroughly discussing the issue. A more thorough hazard identification analysis is needed.
- The TCEQ presumes that an inflammatory response constitutes an "adverse effect" that can properly serve as a point of departure ("POD") for risk assessment. But various events associated with inflammation reflect a protective response of normal, healthy lungs to the

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<sup>1</sup> The Panel consists of trade associations and individual companies that produces or uses silica or silica-containing products and materials, or that perform operations (such as mining) on natural materials that contain crystalline silica. A list of Panel members is attached to this letter as Appendix 1.



- presence of particles, bacteria, pollen, dust and the like. Such normal, transitory “inflammatory” events therefore do not represent an “adverse effect” and should not be used to identify a POD for quantitative risk assessment. Rather, the POD should be based “on pathological changes or their precursors, such as improper repair of damaged lung tissue, scarring, or fibrosis.”
- Contrary to the approach taken in the DSD, there is no evidence that amorphous silica poses a human health risk, and there is no basis for believing that amorphous silica has the same toxic or carcinogenic potency as crystalline silica. Moreover, treating amorphous silica as though it poses the same risks as crystalline silica does not represent sound public health policy.
- The TCEQ’s analysis does not reflect the fact that sufficiently fine (nanosized) silica particles are likely to pose less risk of lung damage than larger (microsized) particles because nanosized particles are more readily diffused and translocated.
- Contrary to the current scientific understanding of lung carcinogenesis, the TCEQ does not document any effects of silica exposure on lung stem cell or progenitor cell populations specifically involved in the development of lung cancer. Moreover, the TCEQ’s dismissal of the hypothesis that silicosis is a necessary risk factor for silica-related lung cancer reflects a misreading (and selective use) of the scientific literature.
- By using point estimates of exposure that ignore the variance of true exposures around the estimated values, the TCEQ has biased upward its estimates of potency (*e.g.*, by using exposure estimates presented in Steenland *et al.* (2001), without correcting for such biases).
- In using Steenland, *et al.* (2001) as the key study for its cancer risk assessment, the TCEQ failed to correct for model specification errors and biases in the Steenland, *et al.* (2001) analysis that render the results of the analysis largely meaningless.

In addition to the appended comments of Dr. Cox, the Panel notes the following in particular regarding TCEQ’s reliance on the Hnizdo, *et al.*, study. In the DSD, the TCEQ calculates a chronic Reference Value and a chronic non-cancer ESL based on data from what it terms the “key study” of South African gold miners by Hnizdo, *et al.* (1993): Risk of Silicosis in a Cohort of White South African Gold Miners. *American J. Indus. Med.* 24: 447-457. In doing so, the TCEQ uses estimates of cumulative (respirable) dust exposure presented by Hnizdo *et al.* (1993) and assumes that the respirable dust for which these exposure estimates are presented had an average quartz content of 30%, as stated in the paper by Hnizdo *et al.* (1993). *See* DSD at 15, 48. The risk assessment was then conducted on that basis, using the resulting respirable quartz values to perform the quantitative analysis. There is a significant problem with this approach.

The respirable dust exposure estimates presented in Hnizdo *et al.* (1993) were for dust particles measured after incineration and acid treatment—or, as Hnizdo *et al.* (1993) describe them, the “incombustible and acid-insoluble dust particles, which include mainly quartz and silicates.” *Id.* at 449. By contrast, as is clear from the paper by Beadle and Bradley (1970), which is referenced by Hnizdo *et al.* (1993) for this point, the 30% quartz content value referred to by Hnizdo *et al.* (1993) and used by the TCEQ was for the respirable dust before incineration and acid treatment.<sup>2</sup> Since the quartz remains in the dust following incineration and acid treatment, the quartz concentration in the incombustible and acid-insoluble dust particles would be higher than it was in the dust prior to being incinerated and acid-treated. As shown by Gibbs & Du Toit (2002), the result of this confusion between dust measurements made after incineration/acid treatment and quartz content determined before incineration/acid treatment is that the estimates of quartz exposure presented by Hnizdo *et al.* (1993) and used by the TCEQ to derive the chronic Reference Value and chronic non-cancer ESL “were probably underestimated by a factor of 1.8”—because the quartz content of the incinerated and acid-treated dust would have been approximately 54%, rather than the 30% value found before incineration/acid treatment.<sup>3</sup> Alternatively, if the 30% quartz content of the dust before incineration and acid treatment is to be used, the measurements of incinerated/acid-treated dust would have to be converted to pre-treatment dust concentrations in order to estimate *respirable silica* exposures in the mines. That conversion would increase the respirable dust values by a factor of approximately 2. *See* Gibbs & Du Toit (2002) at 600.

In sum, when combined with other factors—such as the unrealistic assumption that dust levels did not change between 1936 and 1960—the values presented in Hnizdo *et al.* (1993) and used by the TCEQ are likely to underestimate the actual quartz exposures of the miners in this cohort by a factor of 2. *See* Gibbs & Du Toit (2002).<sup>4</sup> While we do not know the precise impact this underestimation of exposures had on the TCEQ’s risk assessment, preliminary analyses performed by others suggest that the impact is likely to have been very substantial, resulting in a large overestimate of risk.<sup>5</sup>

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<sup>2</sup> *See* Beadle, DG & Bradley, AA (1970): The composition of airborne dust in South African gold mines. In Shapiro, HA (ed): “Pneumoconiosis. Proceedings of the International Conference. Johannesburg 1969.” Oxford: Oxford University Press, pp. 462-466.

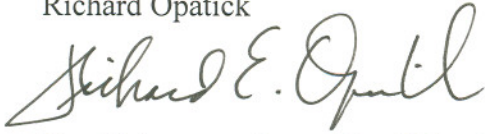
<sup>3</sup> Gibbs, GW & Du Toit, RSJ. Estimating the Quartz Exposure of South African Gold Miners (2002). *Ann. Occup. Hyg.* 46(7): 597-607.

<sup>4</sup> Others have noted the likely underestimation of exposure in the Hnizdo *et al.* (1993) cohort as well. *See, e.g.,* De Klerk, NH *et al.*, A Review of the Australian Occupational Exposure Standard for Crystalline Silica (February 2002, Final Draft for Peer Review) at 35, 40, 49; British Health & Safety Executive, Industrial Chemicals Unit. Respirable Crystalline Silica: Phase I (2001) at 47 (observing that the “key problem” with the Hnizdo *et al.* (1993) study “is that it is limited by substantial weaknesses in the exposure estimates”—including the assumption that measurements taken around 1960 represented exposures in prior decades (which may have been 2-3 times higher), the assumption of a constant 30% quartz content, and the uncertain conversion to gravimetric units).

<sup>5</sup> *See* Gibbs & Du Toit (2002) at 602; Hughes, JM. Radiographic Evidence of Silicosis in Relation to Silica Exposure (1995). *Appl. Occup. Environ. Hyg.* 10(12): 1064-1069 (noting that a twofold underestimation of exposure in the Hnizdo *et al.* (1993) cohort “could account for more than a tenfold overestimation in risk”).

The Panel appreciates this opportunity to comment on the DSD. If you have any questions regarding this submission, please contact me at (703)741-5623, or at [richard\\_opatick@americanchemistry.com](mailto:richard_opatick@americanchemistry.com).

Sincerely,  
Richard Opatick

A handwritten signature in black ink that reads "Richard E. Opatick". The signature is written in a cursive style with a large, sweeping initial "R".

Panel Manager, Crystalline Silica Panel  
American Chemistry Council

**Comments on TCEQ's Proposed Silica Development Support Document  
Submitted by  
Crystalline Silica Panel  
American Chemistry Council**

January 30, 2009

Appendix 1

**Crystalline Silica Panel Companies**

3M

Aggregate Industries

American Foundry Society

Badger Mining Corporation

Brick Industry Association

Fairmont Minerals

Granite Construction, Inc.

Hanson Building Materials America

IDPA

James Hardie Building Products

National Concrete Masonry Association

National Industrial Sand Association

National Stone, Sand & Gravel Association

Omay, Inc.

The Refractories Institute

Unimin Corporation

U.S. Gypsum Company

U.S. Silica Company

**APPENDIX D**  
**Comments submitted for the American Chemistry Council from**  
**Dr. Louis Anthony Cox, Jr.**

# Comments on TCEQ's Proposed Silica Development Support Document

Submitted by  
Crystalline Silica Panel  
American Chemistry Council

January 30, 2009

## EXECUTIVE SUMMARY

The American Chemistry Council's Crystalline Silica Panel ("Panel"), is submitting comments on the Texas Commission on Environmental Quality's (TCEQ) Proposed Silica Development Support Document (DSD), dated September, 2008. The Comments were prepared by Dr. Louis Anthony Cox, Jr. at the request of the Panel. Although the DSD contains much relevant background information on studies of potential risks associated with silica exposures, the Panel believes it fails to provide an appropriate basis for quantitative risk assessments of silica, in the following respects.

1. *No well-developed hazard identification.* The DSD assumes that exposures to the various forms of silica at concentrations that do not exceed  $0.1 \text{ mg/m}^3$  can cause lung cancer and other adverse health effects. That assumption is not self-evidently justified; yet the DSD does not present evidence showing that it is correct (or even thoroughly discuss the issue). Rather, it seems to presume that some risk is present, and focuses on quantifying bounds on the risk.

Before proceeding with quantitative risk assessment, it is usual and desirable to first complete a *hazard identification* that critically reviews evidence – both pro and con – for the hypothesis that exposure causes a non-zero risk that can be further assessed quantitatively. Toward that end, we believe that the DSD should be expanded to present a careful hazard identification analysis for the various forms of silica that it addresses – with a particular emphasis on whether there is evidence of harm to humans at currently permissible levels of exposure.

2. *Definition of adverse effect and POD.* TCEQ defines "inflammation," apparently meaning recruitment of alveolar macrophages and neutrophils into the lung to help clear particles, as

an adverse effect. Exposures that cause such inflammatory responses are used as a point of departure (POD) for risk assessment calculations. But phagocytosis and clearance of particulate matter by alveolar macrophages do not necessarily constitute an adverse effect. Nor does recruitment of macrophages and neutrophils (or other leukocytes) to sites of particulate matter deposition, or accompanying cytokine signaling between macrophages and other leukocyte cell populations. Rather, these events, together with the operation of the mucociliary escalator, are how healthy lungs normally clean and protect themselves despite the ubiquitous presence of particles, bacteria, pollen, dust, and so forth. We therefore believe that the POD should not be based on such normal, transient “inflammatory” events, but rather on pathological changes or their precursors, such as improper repair of damaged lung tissue, scarring, or fibrosis.

3. *There is no evidence that amorphous silica poses a human health risk.* We strongly disagree that exposures to non-crystalline silicas should be treated similarly or identically to exposures to crystalline silica. There are no epidemiological, toxicological, mechanistic, or other scientific grounds for treating amorphous silica as toxic or carcinogenic, or for assuming that it has the same toxic or carcinogenic potency factors as crystalline silica. As far as we know, most other scientific and regulatory bodies that have addressed the issue have rightly concluded that amorphous silica should not be treated the same as crystalline silica; indeed, it is probable (as a well-developed hazard identification section would show) that current exposures to amorphous silica do not pose a human health risk. Nor is it sound risk management policy to treat essentially harmless substances as if they were harmful. This is not “conservative,” as TCEQ claims; rather, it is simply inaccurate. It deprives risk managers of the valid scientific risk assessment information needed to support effective risk management resource allocation decisions.
4. *The particle size-dependency of toxicity for crystalline silica is not treated correctly.* Instead of assuming that all sufficiently small crystalline silica particles have the same potency for harming human health, TCEQ’s proposal should be revised to reflect the fact that sufficiently fine (nanosized) particles probably pose *less* risk of fibrosis (and resulting harm) than larger particles – due to the fact that they are more readily diffused and translocated.
5. *Using point estimates of cumulative exposures (mean or total), while ignoring the variance of true exposures around the estimated values, biases potency estimates upward. TCEQ should correct its potency estimates for this source of bias.* If the frequency distribution of daily exposures remains fixed over time, then cumulative exposure is a random variable

(approximately normally distributed, for long exposure durations). For any estimated mean cumulative exposure, silicosis and lung cancer cases are expected to occur disproportionately (and perhaps exclusively) among individuals with greater-than-estimated exposures. This biases upward potency estimates based on estimated mean cumulative exposures. To obtain unbiased potency estimates, TCEQ needs to correct for this bias in the sources (e.g., Steenland *et al.*, 2001) that it has used.

6. *TCEQ has not documented any effects of silica exposures on lung stem cells involved in the development of lung cancer.* Rather, TCEQ has discussed (largely conjectural) possible effects in terminally differentiated cells that cannot progress to cancer. TCEQ's discussions of silica-related lung cancer MOAs should be revised to reflect current knowledge of lung carcinogenesis, and to acknowledge that there is no evidence that silica exposures of any type cause lung cancer at concentrations below those that cause fibrosis and silicosis.
7. *TCEQ's use of Steenland et al. (2001) as a key study does not correct for model specification errors and biases in Steenland et al.'s analysis.* The modeling approach used by Steenland *et al.* (2001) creates the appearance of a "statistically significant" positive association between any two positive random variables, even if statistically they are completely independent of each other. The results of Steenland *et al.* (2001), therefore, are meaningless, insofar as they result only from the authors' modeling assumptions, rather than from any clear patterns in the data analyzed. Data from other larger, more recent studies should be used instead, and they should be analyzed using biologically-based models that are specifically appropriate for assessing lung cancer risks.

The following line-by-line comments develop these and closely related points in greater detail.

***Page 6, line 36. "The critical effect of acute exposure to silica is increased inflammation and cytotoxicity in the respiratory tract."***

*Comment: Definition of "critical effect."* Increased markers of inflammation and cytotoxicity (such as macrophage activation and neutrophil recruitment) in respiratory tracts in response to particulate exposures do *not* necessarily indicate a pathological state or any harm or injury. To the contrary, in the lungs, many aspects of transient inflammation and cytotoxicity are not *adverse* effects, but a normal and expected part of homeostasis for animals in non-sterile environments.

An important part of the normal, healthy function of the respiratory tract is to clear inhaled particulate matter, for example, via activation of alveolar macrophages and recruitment of neutrophils. Toxicologists have understood for decades that “A transient increase in the number of phagocytizing cells recruited into the lower respiratory tract is an obligatory response to a sufficiently considerable deposit of inhaled or injected particles,” and that this is just a part (albeit an important one) of the normal “physiological mechanism of pulmonary dust clearance” (e.g., Katsnelson and Privalova, 1984, p. 322, [www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1568354](http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1568354))<sup>1</sup>. Increased markers of inflammation and cytotoxicity in this context do *not* indicate an unhealthy response or an adverse effect. They are not even precursors of adverse effects, but simply indicate normal, healthy functioning. Hence, they do not represent a “critical effect,” in the sense of being “The first adverse effect, or its known precursor, that occurs as the dose rate increases” (<http://iter.ctcnet.net/publicurl/glossary.htm>)<sup>2</sup>.

To qualify as a “critical effect,” some evidence of a response that is not entirely consistent with perfect health (such as persistent, *unresolved* inflammation) is needed. Increased inflammation and cytotoxicity may simply be biomarkers of exposure, not of any adverse effects. Indeed, Warheit et al. (1995) explicitly state that “Amorphous silica produced a *transient* pulmonary inflammatory response, and Ludox [colloidal silica] elicited *transient* pulmonary inflammatory responses at 50 or 150 mg., but not at 10 mg. After three months most of the biochemical values of the Ludox-exposed animals had *returned to the control level.*” (Emphasis added.) (Warheit DB, McHugh TA, Hartsky MA. [Differential pulmonary responses in rats inhaling crystalline, colloidal or amorphous silica dusts](#). *Scand J Work Environ Health*. 1995; 21 Suppl 2:19-21.)<sup>3</sup> Such responses do not indicate pathology. As TCEQ acknowledges (lines 21-23 of p. 14), “[S]ome data indicate that exposure to amorphous silica leads to transient pulmonary changes but not to chronic conditions, such as fibrosis.” Indeed, we would go further: *no credible data indicate that currently permitted exposures to amorphous silica cause any human health harm whatsoever*. Thus, for example, industry experts in other countries have concluded from such data that “*synthetic amorphous silica may be judged as obviously nontoxic when used at currently applied levels*” (emphasis added, [www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/rdonlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological\\_Overview\\_Amorphous\\_Silica\\_in\\_Working\\_Environment.pdf](http://www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/rdonlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological_Overview_Amorphous_Silica_in_Working_Environment.pdf))<sup>4</sup>.

By contrast, sufficiently high exposures to crystalline silica “produced persistent pulmonary inflammatory responses characterized by neutrophil recruitment and consistently

elevated biomarkers of cytotoxicity in bronchoalveolar lavage fluids, and progressive histopathological lesions were observed within one month of the exposure.” (Warheit et al., 2005, *op cit.*) This is indeed a pathological response, and hence a good candidate for a critical effect of crystalline silica in the CD rats used in the study. But it is quite different from the responses for non-crystalline silica.

*Recommendation:* Redefine the critical effect as an unhealthy or adverse response (such as persistent, unresolved inflammation), or as a precursor condition that progresses to an adverse response, rather than as a normal, healthy response (transient inflammation and cytotoxicity as part of normal clearance of particulate matter from the lungs).

*Comment: Use of unvalidated animal models.* Animal models do not necessarily provide valid models for human lung diseases (*see e.g.*, Wright JL, Cosio M, Churg A. [Animal models of chronic obstructive pulmonary disease](#). *Am J Physiol Lung Cell Mol Physiol*. 2008 July; 295(1):L1-15)<sup>5</sup>. Before using an animal (*e.g.*, rat) model as a basis for risk analysis of human health, it should be validated for such use by showing that the animal and human disease models share relevant mechanisms and responses. Chapter 3 of the DSD does not present any evidence that rats provide a valid animal model for human silicosis.

*Recommendation:* Add a discussion of the validity of the rat response to crystalline silica exposures, as a model for human responses.

**Page 6, lines 40-41. “The TS made a policy decision to apply one set of acute toxicity factors to all forms of silica, noting that this approach is likely conservative.”**

*Comment: Assigning one toxicity factor to different forms of silica undermines the basis for rational and effective health protection and risk management.* The NIOSH-recommended exposure limits for crystalline silica and amorphous silica differ by a factor of over 100, as described on p. 6, line 29 of the DSD. Based on experimental data, including Warheit *et al.*, 1995, *op cit*, it is well known that, in reality, “crystalline silica dust is more potent in producing pulmonary toxicity when compared with amorphous or colloidal silica particles.” Similarly, a recent review of “Silica exposure and its effects on the physiology of workers” from the Republic of South Africa, where mining is a major industry, noted that “Quartz, cristobalite and

tridymite have the highest potential to introduce fibrosis in the lungs. *The biological reactivity of the three types of crystalline silica is not similar. Quartz potential to induce fibrosis is higher than tridymite and tridymite's potential to induce fibrosis is higher than cristobalite*" (emphasis added) <http://www.labour.gov.za/documents/useful-documents/occupational-health-and-safety/silica-exposure-and-its-effect-on-the-physiology-of-workers>.<sup>6</sup>

If amorphous silica is much less toxic than crystalline silica, as indicated in numerous studies, then the Toxicity Section's "policy decision" to treat them as if they had the same toxicity is not "likely conservative," in the sense of protecting workers or public health. It is simply inaccurate. The policy and risk management consequences of treating different substances as if they had the same toxicity, when in reality they do not, can be to make allocations of limited risk management resources extremely inefficient (worse than random) (Cox LA Jr, Popken DA. [Some limitations of aggregate exposure metrics](#). *Risk Analysis* 2007 Apr;27(2):439-45.)<sup>7</sup>

*Recommendation:* Develop separate toxicity factors for different forms of silica (including amorphous, colloidal, and crystalline) that have significantly different toxicities in experimental studies. Form-specific toxicity factors should take into account form-specific data (such as the NOEL of 10 mg/m<sup>3</sup> reported for colloidal silica, Warheit DB, Carakostas MC, Kelly DP, Hartsky MA. [Four-week inhalation toxicity study with Ludox colloidal silica in rats: pulmonary cellular responses](#). *Fundam Appl Toxicol*. 1991 Apr;16(3):590-601.)<sup>8</sup>

***Page 7, lines 13-15. "...[N]atural amorphous silica may contain up to 60% crystalline silica by weight. Therefore, the toxicity values developed in this document apply to crystalline and amorphous silicas and their byproducts."***

*Comment: Non-sequitur reasoning.* The "therefore" in this passage does not seem to be logically justified. (For example, table salt "contains" both chlorine and sodium, but it would be foolish to apply the same toxicity value for chlorine to table salt.) The fact that one substance (of very low toxicity) may sometimes be found mixed with another substance of greater toxicity does not warrant the conclusion that the first substance (or a mixture of the two substances) has the same toxicity value as the second substance.

**Page 7, lines 17-23. “...[T]oxicity is restricted to particles that are small enough to be deposited into the target regions of the respiratory tract. ...[T]he acute toxicity factors developed will apply to all silica particles less than or equal to the median cut point for the thoracic region of 10 µm.”**

*Comment: Important particle transport and size factors affecting cytotoxicity have been omitted.*

Toxicity of crystalline silica depends not only on where particles are *deposited*, but also on where and how they are *transported* within the respiratory tract, e.g., during clearance (see e.g., Kilburn KH, [Particles causing lung disease](#). *Environ Health Perspect.* 1984 Apr; 55:97-109.

<http://www.ehponline.org/members/1984/055/55009.PDF>.)<sup>9</sup> Moreover, it has been demonstrated experimentally that sufficiently small silica particles have significantly *less* toxicity than larger ones in causing lung fibrogenesis following intratracheal instillation:

“At 2 months after instillation, there were still Stage I of silicotic nodules in nanosized SiO<sub>2</sub> group. In microsized SiO<sub>2</sub> group mainly Stage II+, III of silicotic nodules were found. Quantity image analysis showed that the expressions of IL-4 and TGF-beta1 in nanosized SiO<sub>2</sub> groups were significantly lower than those in microsized SiO<sub>2</sub> groups (P < 0.01), but without significant difference from those of saline control groups. Our experiment revealed that the effect of fibrogenesis of nanosized SiO<sub>2</sub> might be milder than that of microsized SiO<sub>2</sub> in rats, potentially resulting from nanoparticles tending to be diffused and easily translocated due to their ultrafine particle size compared to microsized particles.” (Chen Y, Chen J, Dong J, Jin Y. *Toxicol Ind Health.* 2004 Jun;20(1-5):21-7. [Comparing study of the effect of nanosized silicon dioxide and microsized silicon dioxide on fibrogenesis in rats.](#))<sup>10</sup>

Thus, the assumption that the same acute toxicity factor “will apply to all silica particles less than or equal to... 10 µm” does not appear to be well supported by available evidence.

*Recommendation:* Treat fibrosis, rather than delayed recruitment of neutrophils and increased BALF LDH, as the critical effect. Acknowledge that only a restricted range of SiO<sub>2</sub> particle sizes (neither too large nor too small) causes this critical effect in rats.

**p. 14. lines 29-32. “Although the lack of nodular fibrosis and reduced pulmonary function following exposure to amorphous precipitated silica may indicate that its toxicity is not as great as other forms of silica, TS believes the application of the chronic toxicity factor derived from quartz to all forms of silica is not overly conservative.”**

*Comment:* Criteria for “overly conservative” are not stated. “May” should be removed from the above. Treating amorphous silica as having the same toxicity as quartz is inaccurate, conflicts with overwhelming evidence to the contrary, and undermines the basis for sound, rational risk management decisions and resource allocation.

*Recommendation:* Develop a separate toxicity factor for quartz, and acknowledge that amorphous silica at current exposure levels shows no evidence of toxicity.

***p. 15, lines 39-40. Cumulative dust exposure was calculated up to the onset of silicosis or the end of exposure...***

*Comment:* Cumulative dust exposure has not been validated as the exposure metric that best predicts risk, nor has it been validated as a metric that measures the aspects of exposure that actually cause risk of adverse health effects. Studies of diesel exhaust in rats suggest that exposure conditions creating lung overburden are essential for some harm (including lung cancer) to occur at all (Valberg and Crouch, 1999, <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1566471>.)<sup>11</sup> Estimated cumulative dust exposure may be strongly *correlated* with unobserved conditions (e.g., transient high exposure episodes) that actually cause harm, even if the estimated cumulative exposure level itself is harmless.

More generally, using estimated mean concentration levels can bias estimated potencies upward, by attributing to the *estimated* exposure concentrations the harm actually caused by *higher-than-estimated* exposure concentrations. Indeed, when only estimated mean concentrations are used, and the variance of true concentrations around their estimated mean value is ignored (as on line 42 of page 15, or line 18 of page 16 of the DSD), then *estimated potencies are necessarily biased upward* (provided that true exposures have positive variance around the estimated levels, and that higher exposure levels are more harmful than lower ones.) The reason is that, for any estimated level of exposure, adverse health effects are more likely to have been caused by higher-than-estimated true exposures than by lower-than-estimated true exposures. TCEQ should correct its potency factors and risk estimates for this source of bias.

*Recommendation:* Develop statistical exposure models of the positive correlation between estimated *cumulative* exposure and the likely extent of *higher-than-estimated* exposures (e.g., by using a central limit theorem for cumulative exposures, together with estimates of exposure concentration variances or standard deviations, as on p. 15, line 45 of the DSD). Reduce risk estimates to account for the effects of non-zero variance of true exposures around estimated exposures. (This reduction is needed to avoid attributing to estimated exposure levels the health impacts of higher-than-estimated exposures.)

***p. 16, lines 31-32. “Chronic inflammation is believed to be the primary mechanism of silicosis/fibrosis associated with long-term silica exposure.”***

*Comment: Incorrect MOA.* Chronic inflammation itself is not a “primary mechanism of” fibrosis; it may be necessary, but is not sufficient. Rather, *improper repair* of damaged lung tissue (such as degradation of collagens in the ECM due to sustained disruption of protease-antiprotease balance) is essential for fibrosis. Exposures that cause chronic inflammation but not improper repair of damage to lung tissue should not be expected to cause fibrosis.

***p. 17, lines 26 and 27: “Therefore, the model with the lowest AIC value (log-probit) was selected as the best fitting model.”***

*Recommendation:* Use Bayesian model averaging (BMA) to account for model uncertainty, rather than selecting one model and ignoring model uncertainty.

***p. 22, lines 12 and 39-41. “[T]hose [studies] that did consider confounding found no relationship between silica exposure and lung cancer. ... Because the evidence is inadequate and studies do not indicate that natural and synthetic amorphous silicas are not carcinogenic, the TS conservatively chose to apply the <sup>chronic</sup>ESL<sub>linear(c)</sub> to all forms of silica.”***

*Comment: Improper application of cancer risk assessment to a non-carcinogen in the absence of evidence of carcinogenicity.* TCEQ appears to be arguing that, because it is impossible to empirically prove a negative, they can choose to treat essentially any substance, even SAS, as a carcinogen. As the discussion on p. 22, lines 6-34 of the DSD suggests, it far from clear whether even occupational exposures to *crystalline silica* cause human lung cancer, particularly in the

absence of silicosis. When confounding is controlled and conflicting study results are considered, there is no clear evidence that exposure to crystalline silica increases the risk of lung cancer, even at occupational exposure levels. Therefore, to assume that even crystalline silica poses a carcinogenic public health threat to the general population at concentrations much lower than occupational levels is very speculative. (This is why we believe that a well-researched hazard identification section should be added – it may be that there is no public health risk to assess.) To then treat *amorphous* silica as a carcinogen, because “studies do not indicate that natural and synthetic amorphous silicas are not carcinogenic,” adds another leap of logic that seems to go well beyond rational scientific interpolation or extrapolation from relevant data. To our knowledge, no epidemiological, toxicological, clinical, or mechanistic data support implicating amorphous silica as a human lung carcinogen. No other scientific or regulatory body that we know of has identified amorphous silica as a human lung carcinogen, or has concluded that it should be regulated as such. TCEQ could equally well (or equally badly) argue that “studies do not indicate that water is not carcinogenic,” and proceed to regulate water as a carcinogen.

*Comment: The decision to treat amorphous silicas as carcinogenic is not justified by a valid appeal to “conservatism”.* It is not necessarily conservative (in the sense of leading to priorities and risk management decisions that protect public or occupational health) to pretend that substances are carcinogenic if they are not, or to treat substances with very different potencies as if they had the same potency. In general, using such simplifying assumptions in risk assessment deprives risk managers of the information that they need to make effective resource allocation decisions to protect human health. The result can be distorted risk management decisions that are worse than useless (e.g., less effective than purely random decision making) in reducing risks and protecting and promoting health (Cox and Popken, 2007, *op cit.*).

*Comment: The TS’s decision to apply the same <sup>chronic</sup>ESL<sub>linear(c)</sub> to all forms of silica is inconsistent with biological knowledge.* For example, “an association between carcinogenic and fibrogenic potency has been observed in various animal species exposed to crystalline silica” (Pairon JC, Brochard P, Jaurand MC, Bignon J., [Silica and lung cancer: a controversial issue](#). Eur Respir J. 1991 Jun;4(6):730-44.)<sup>12</sup> It is therefore reasonable to expect that forms of silica and/or exposure histories with very different fibrogenic potencies will present significantly different carcinogenic risks.

*Comment: The decision to treat amorphous silica as carcinogenic is not justified by data or biological evidence.* The TS states that “studies do not indicate that natural and synthetic amorphous silicas are not carcinogenic.” We would like to better understand: What criteria or evidence (if any) *would* the TS accept as indicating that amorphous silicas are not carcinogenic? To the best of our knowledge, no epidemiological or experimental study suggests that exposures to amorphous silica *are* carcinogenic. It remains true that, “With regard to carcinogenicity, there is no evidence in the literature for an association between the exposure of workers to synthetic amorphous silica and lung cancer development or mortality. ... According to current epidemiological data, there is no evidence of lung cancer or other long-term respiratory health defects in workers employed in the production of synthetic amorphous silica.” [www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/rdonlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological\\_Overview\\_Amorphous\\_Silica\\_in\\_Working\\_Environment.pdf](http://www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/rdonlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological_Overview_Amorphous_Silica_in_Working_Environment.pdf).<sup>13</sup> To require proof of the negative when there is no evidence of the positive represents neither sound science nor sound public policy.

Acknowledging that absence of evidence would not constitute evidence of absence, we nonetheless believe that examining causal mechanisms of lung carcinogenesis following excessive exposure to particulate matter provides *positive evidence of absence* – that is, evidence against the hypothesis that exposure to amorphous silica poses a non-zero risk of lung cancer. For example, studies of lung carcinogenesis induced by exposures in experimental animals have indicated that, “[T]he crucial matter [for development of lung cancer] seems to be prolonged retention of carcinogens at a site by particle[s], and the failure of these cells to be exfoliated in their normal time.” Even significant damage to the epithelium (for example, from brief exposures to cigarette smoke) *does not produce tumors*, unless exposure intensity and duration are great enough to activate other mechanisms (such as squamous metaplasia) that prevents the normal exfoliation of damaged and dysplastic cells (Kilburn KH, [Particles causing lung disease. Environ Health Perspect.](http://www.ehponline.org/members/1984/055/55009.PDF) 1984 Apr; 55:97-109, p. 102. [www.ehponline.org/members/1984/055/55009.PDF](http://www.ehponline.org/members/1984/055/55009.PDF).)<sup>14</sup> From this perspective, exposures that do not impair normal exfoliation of damaged cells – including exposures to amorphous silicas – are not expected to cause tumors.

Although it is certainly possible and desirable to add more mechanistic detail to discussions of particle-induced lung carcinogenesis, we believe that considering what *is* already

known provides solid evidence against the hypothesis that amorphous silica is a human lung carcinogen at currently allowed exposure levels.

*Recommendation:* Do not apply the  $^{chronic}ESL_{linear(c)}$  to amorphous or colloidal forms of silica, as there is no epidemiological or toxicological evidence that they are carcinogenic; there is no biological evidence that they cause the changes needed to induce lung cancer; and, indeed, there is mechanistic evidence against this hypothesis.

*Recommendation:* Acknowledge that different forms of silica (including amorphous, colloidal, and crystalline) have significantly different fibrogenic potencies in experimental studies, and that there is no scientific basis for assigning a cancer risk factor to non-crystalline silicas. TCEQ has offered no toxicological, epidemiological, clinical, or mechanistic studies establishing that exposure to non-crystalline silicas increases the risk of lung cancer. Regulating all forms of silica as if they were known to be carcinogenic is not warranted by sound science or by sound risk management principles. It appears to reflect an unjustified desire to regulate, in the absence of any hazard identification showing that regulation is expected to create positive public health benefits.

***p. 22, lines 43-44. “While a detailed carcinogenic MOA for silica is not available, several potential MOAs exist, including direct genotoxicity and cell proliferation secondary to chronic inflammation.”***

*Comment:* The TS’s suggested “potential MOAs” appear to be very general speculations, not specifically addressing, or appropriate for, lung carcinogenesis and silica. Biologically motivated risk models have been developed specifically for lung cancer risk and have been validated with epidemiological and experimental data for several cohorts and various carcinogens (e.g., Jacob V, Jacob P. [Modelling of carcinogenesis and low-dose hypersensitivity: an application to lung cancer incidence among atomic bomb survivors](#). *Radiat Environ Biophys*. 2004 Feb;42(4):265-73 <sup>15</sup>; Hazelton WD, Moolgavkar SH, Curtis SB, Zielinski JM, Ashmore JP, Krewski D. [Biologically based analysis of lung cancer incidence in a large Canadian occupational cohort with low-dose ionizing radiation exposure, and comparison with Japanese atomic bomb survivors](#). *J Toxicol Environ Health A*. 2006 Jun; 69(11):1013-38 <sup>16</sup>; Cox LA Jr., [Could Removing Arsenic from Tobacco Smoke Significantly Reduce Smoker Risks of Lung](#)

Cancer? *Risk Analysis* 2009. 29(1):3-17)<sup>17</sup>. These lung cancer-specific risk models indicate that *risk of lung cancer is increased by proliferation of initiated stem cells, not proliferation of fully differentiated cells* (e.g., macrophages and neutrophils) secondary to chronic inflammation. Similarly, in contemporary biological research, NIH (2007) notes that “Any consideration of inflammation and the tissue microenvironment in the development of lung cancer *must also include the effects of the altered microenvironment on lung stem cells themselves*” (emphasis added). (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-046.html>)<sup>18</sup>

The TS’s discussion of “potential MOAs” in Section 4.2.1 refers only to effects in alveolar epithelial cells, human embryonic lung fibroblasts, and sputum. No effect in any target cells of interest for lung carcinogenesis (such as the BASCs, *ibid*) has been described or discussed. The effects described by the TS in these cell populations (and sputum) are therefore not truly “potential MOAs” for silica-induced lung cancer, as they do not refer to evidence of silica-induced changes in relevant lung cell populations and present no evidence of any relation between silica exposure and recognized biomarkers of increased lung cancer risk (such as LOH 3p). (One could use reasoning like this to speculate that any substance, including pure water, is a human lung carcinogen. For water, one might postulate that disassociated hydroxyl radicals generate reactive oxygen species (ROS) in the lung that trigger proliferative signaling cascades and ultimately interfere with normal DNA replication and apoptotic removal of pre-malignant cells. A problem with such general speculative discussions of “potential MOAs” is that they have no known relevance to real risks, target cells, biomarkers for lung cancer risk, or actual carcinogenic or pre-carcinogenic damage relevant for or predictive of increased risk of lung cancer. They are “weight-of-imagination”, not “weight-of-evidence”.) The nonlinear MOA for lung cancer discussed in section 4.2.3.5. p. 27, is much more biologically relevant, but current evidence (discussed below) is that potential silica-related lung cancer occurs only in the presence of silicosis.

Likewise, the discussion of “direct genotoxicity,” free radical production, interference with DNA replication and repair, MAPKs, CDK4, etc. toward the end of Section 4.2.1 does not provide relevant information specifically focused on *lung stem cells, lung carcinogenesis, or biomarkers of increased lung cancer risks*. Of course, one expects to see effects of toxic doses of almost anything, including non-carcinogenic particulates, on some cell signaling cascades and cell behaviors (such as mitotic cycle check points). That is essentially what it means for something to have a toxic effect in cells. But such changes *per se* are not evidence for a

mechanism of carcinogenicity unless relevant end points or biomarkers in relevant cell populations are involved.

By the same token, although some conditions that involve chronic *unresolved* inflammation (specifically, COPD) are indeed associated with significantly increased risk of lung cancer, this association holds only for patients with well-developed pathologies. Thus, we do not agree that “cell proliferation secondary to chronic inflammation” *per se* is a known or credible MOA for silica-related lung cancer.

*Recommendation:* Revise the discussion of MOAs to present evidence related to lung cell populations, effects, and biomarkers that are *specifically relevant to lung cancer risk*. Discuss in detail the conclusion, from others, that “Occupational exposure to silica can result in silicosis with a small increased risk for lung cancer, but without silicosis there is no increased risk.” (<http://info.cancerresearchuk.org/cancerstats/types/lung/riskfactors/>)<sup>19</sup> Unless the TS provides valid scientific reasons for rejecting this conclusion, its discussion of the MOA should emphasize thresholds for degenerative lung disease leading to increased lung cancer risk, incorporating specific, biologically relevant information about silica-induced lung disease (e.g., <http://www.cdc.gov/niosh/nas/RDRP/ch3.2d.htm>)<sup>20</sup>.

***p. 23, lines 20-21. “However, more recent evidence indicates that silicosis is not a risk factor for lung cancer.”***

*Comment:* This is an incorrect and highly selective interpretation of the cited sources, and it runs counter to the preponderance of scientific evidence, which indicates that silicosis likely is a necessary risk factor for silica-related lung cancer. The TS has cited only three studies (Checkoway et al. 1999, Chen and Chen 2002, and Yu et al. 2007) to support its claim that silicosis (for which there is an exposure threshold) is *not* a risk factor for lung cancer in silica-exposed workers – the implication being that exposure to silica dust (without an exposure threshold) *is* a risk factor for lung cancer independently of silicosis. Checkoway et al. (1999) does not support this proposition, for several reasons. First, the SMR for lung cancer mortality among silicotic workers in that study was higher than the SMR for workers without silicosis. Moreover, the number of workers with radiological silicosis (81) and the number of lung cancer deaths among such workers (4) were too small to reach any precise statistical conclusions. Silicosis status at the time lung cancer was diagnosed was not ascertained. Finally, information

on possible confounding by cigarette smoking was limited in this study, and the findings differed from findings in other studies – thus, as the author’s acknowledge, the “role of silicosis in lung cancer is likely to remain controversial.”

Chen and Chen (2002) also do not support the claim that silicosis is not a necessary risk factor for potential silica-related lung cancer. While Chen and Chen found that silicosis did not seem “to be related to the increased risk of lung cancer” observed in certain Chinese tin miners, their findings also provided “little support for the hypothesis that respirable crystalline silica induces lung cancer.” Similarly, Yu *et al.* (2007) did not find a link between silicosis and lung cancer; but nor did they find a link between “*silica dust . . . and lung cancer,*” leading the authors to conclude that the classification of crystalline silica “as a human lung carcinogen might need to be reviewed.” (Emphasis added.) In more detail, Yu *et al.* explained:

“The increase in lung cancer mortality became very limited in our entire cohort (12%), in particular among surface construction workers (9%) after adjusting for smoking. As no good local data on the risk of lung cancer were available separately for current smokers and ex-smokers, our indirect adjustments were only done with information on ever smokers. Hence, they could only be considered as best estimates of the possible magnitude of the confounding effects due to smoking. . . . Evidence on exposure–response relationship between radiological severity of silicosis and lung cancer was far from being consistent. . . . Potential misclassification between large opacities of silicosis and lung cancer could not be ruled out. . . . **In conclusion, results from our cohort study did not offer positive support to a link between silica dust or silicosis and lung cancer** after taking into consideration the confounding effects of cigarette smoking, socioeconomic class, and concomitant occupational exposures to other lung carcinogens (by restricting the analysis to the subgroup of surface construction workers with no exposures to other carcinogens). The poor exposure–response relationship with the various exposure indices and the radiological severity also did not offer support for a causal link. The classification of silica dust as a human lung carcinogen might need to be reviewed.” (Emphasis added.)

<http://annonc.oxfordjournals.org/cgi/content/full/18/6/1056><sup>21</sup>

Thus, Yu *et al.* does not support the proposition that silica dust should be viewed as a non-threshold lung carcinogen.

The TS does not consider in any detail the large-scale review of recent epidemiological studies by Pelucchi *et al.*, 2006, which is more recent and larger than the 1999 and 2002 studies of Checkoway *et al.* and Chen and Chen. (For case-control studies, Pelucchi *et al.*, reported that “The RRs were 3.27 in case-control studies of silicotics only, 1.41 in studies where silicosis

status was undefined and 0.97 among non-silicotic subjects.”) This study offers strong evidence against the TS’s dismissal of silicosis as a necessary risk factor for silica-related lung cancer.

A contemporary perspective on the question (Erren *et al.*, 2008) is as follows:

“Importantly, our detailed examination of 11 studies of lung cancer silica-exposed individuals without silicosis included only three with data allowing adjustment for smoking habits. **They yielded a pooled RR estimate of 1.0** [95% CI = (0.8-1.3)]. The other eight studies, with no adjustment for smoking habits, suggested a marginally elevated risk of lung cancer [RR = 1.2; 95% CI (1.1-1.4)], but with significant heterogeneity between studies (P approximately 0.05).” (Emphasis added.) (Source: *Int Arch Occup Environ Health*. 2008 Dec 6; <http://lib.bioinfo.pl/pmid:19066933>.)<sup>22</sup>

In sum, the weight of evidence supports the following conclusion: “Occupational exposure to silica can result in silicosis with a small increased risk for lung cancer, but *without silicosis there is no increased risk.*”

(<http://info.cancerresearchuk.org/cancerstats/types/lung/riskfactors/>)<sup>23</sup> (emphasis added).

*Recommendation:* Withdraw the assertion that “*more recent evidence indicates that silicosis is not a risk factor for lung cancer*” – with its implication that silica dust exposure in the absence of silicosis is such a risk factor. This is an over-interpretation (and misinterpretation) of a subset of available data, and is directly contradicted by the recent, large study of Pelucchi *et al.*, 2006. NIOSH and other scientists specializing in silica and lung cancer do not agree that it can now be concluded that silicosis is not a risk factor for lung cancer (<http://www.cdc.gov/niosh/nas/RDRP/ch3.2d.htm>)<sup>24</sup>; to the contrary, it seems likely that silica does not cause lung cancer unless silicosis is present. This is consistent with recent mechanistic data (Jin, Z *et al.*, [Identification of differentially expressed genes in rat silicosis model by suppression subtractive hybridization analysis](#). *Acta Biochim Biophys Sin*. 2008 Aug;40(8):740-6.)<sup>25</sup>

*p. 23, lines 29-30. Steenland et al., (2001) pooled exposure-response data from ten of these studies.*

*Comment:* Steenland *et al.*, pooled exposure estimates, not exposure data. It is misleading to state that Steenland *et al.*, pooled exposure-response data, when what they really did was to use

retrospective *estimates* of exposure. (In their words, “Quantitative exposure estimates by job and calendar time were adopted, modified, or developed to permit common analyses.”) From a statistical standpoint, this makes an important difference, because *unmodeled errors in exposure estimates can create apparently “significant” associations between estimated exposure and response variables, even when there is no true relation between them*, and even if the absence of a significant relation would be obvious if actual measurements (“data”) were used.

Steenland *et al.* wrote that “the exposure estimates were reasonably successful in estimating exposure, in as much as a positive and reasonably monotonic exposure-response trend was observed” for silicosis mortality (quoted on p. 22, lines 43-35 of the DSD). However, *both the mean and the error variance* of estimated cumulative exposures (but not the variance of actual cumulative exposures, which is zero) increase with increasing exposure duration. Therefore, a positive monotonic trend could occur even if silica plays no role, or if the true dose-response relation has a concentration-and-duration threshold. Observing such a trend does not discriminate among alternative risk models (e.g., threshold vs. non-threshold) or establish that silica exposure, rather than age and duration in the work place, increase the risk of lung cancer.

***p. 23, lines 30-33. “The individual studies each have limitations.... However, the pooled data account for exposure to different forms of crystalline silica at different concentrations and were deemed by the TS as the most appropriate data set for developing the <sup>chronic</sup>ESL<sub>linear(c)</sub>.”***

*Comment: We question whether the pooled data developed by Steenland et al. (2001) really are “appropriate” for calculating a cancer-based chronic ESL for all forms of silica. The studies considered by Steenland et al. generally did not correct for well-known modeling biases (see Table 1) that can provide non-causal explanations for reported exposure-response associations. To be “appropriate” for regulatory risk assessment, a study should apply appropriate statistical methods (e.g., right column of Table 1) to test, refute, eliminate, or correct for, potential biases in the left column. These criteria reflect widely accepted aspects of epidemiological methodology. By these criteria, we believe that the Steenland et al. (2001) study does not provide an “appropriate” data set for developing the <sup>chronic</sup>ESL<sub>linear(c)</sub>.*

*Comment: Why does TS use the Steenland et al. (2001) study but not the more recent, studies reviewed by Pelucchi et al. (2006)? Based on their “systematic review of epidemiological investigations on silica exposure and lung cancer risk published after the IARC Monograph,*

including 28 cohort, 15 case-control and two proportionate mortality ratio (PMR) studies,” Pelucchi *et al.* (2006) concluded that “The RRs were 1.69 in cohort studies of silicotics only, 1.25 in studies where silicosis status was undefined and 1.19 among non silicotic subjects. ... The RRs were 3.27 in case-control studies of silicotics only, 1.41 in studies where silicosis status was undefined and 0.97 among non silicotic subjects.”

(<http://annonc.oxfordjournals.org/cgi/content/full/17/7/1039>)<sup>26</sup> In other words, this relatively recent meta-analysis provides support for the hypothesis that exposure to crystalline silica increases lung cancer risk among patients with silicosis, but not necessarily among patients without it. (The interpretation of RRs less than 2 requires careful attention to issues such as those in Table 1 before clear causal interpretations and valid causal inferences can be drawn.)

TABLE 1: Potential Non-Causal Explanations for Associations, and Some Statistical Methods to Overcome Them.

Potential Non-Causal Explanations	Statistical Methods to Refute Potential Non-Causal Explanations
<b>Modeling Biases</b>	(See <a href="http://cran.r-project.org/">http://cran.r-project.org/</a> for more on statistical methods and R software.)
Variable selection bias (includes selection of covariates in model)	Bootstrap variable selection, Bayesian model averaging (BMA), and cross-validation for variable selection (Wang <i>et al.</i> , 2004).
Omitted explanatory variables (including omitted confounders)	Include potential confounders in an explicit Bayesian network or causal graph model; test for unobserved latent confounders
Variable coding bias. (Coding of variables may affect risk estimates. See Streiner 2002, Brenner & Loomis 1994)	Don't unnecessarily discretize continuous variables (Royston <i>et al.</i> , 2005, Gustafson & Le 2002, Ragland, 1992). Use automated variable-coding methods such as classification trees (see Chapter 6).
Aggregation bias/Simpson's paradox	Test hypothesized causal relations at multiple levels of aggregation, down to individual-level data.
Multiple testing/comparisons bias	Adjust p-values (Romano and Wolf, 2005)
Choice of exposure and dose metrics.	Use multiple exposure indicators as explanatory variables (e.g., concentration and time. Don't combine them.)
Choice of response/effect metrics	Use survival functions & transition rates among health states.
Model form selection bias; uncertainty about correct model	Use flexible non-parametric models (e.g., kernel smoothers, wavelets) and BMA for multiple models. Report model diagnostics and sensitivities of results to model forms (Greenland, 1989).
Missing data (Little and Rubin 1987; Horton 2007)	Use data augmentation, EM, multiple imputation (Harrell 2007), or Markov Chain Monte Carlo (MCMC) algorithms (Schafer, 1997)
Measurement and misclassification errors in explanatory variables	Use Bayesian measurement error models; treat unknown true values as missing data (Schafer, 1997; Ibrahim <i>et al.</i> , 2005); use bias-correction formulas, regression-calibration, instrumental variables, simulation-extrapolation (SIMEX) corrections (Carroll <i>et al.</i> , 2006) or Bayesian smoothing and regression splines (Berry <i>et al.</i> , 2002)
Unmodeled heterogeneity in individual response parameters	Use latent variable models, finite mixture distribution models, or frailty models of inter-individual variability. ( <a href="http://cran.r-project.org/">http://cran.r-project.org/</a> )
Biases in interpreting and reporting results	Report results (e.g., posterior PDFs) <i>conditioned</i> on data, models, and statistical methods. Show sensitivities.
<b>Sample Selection Biases</b>	
Sample selection (sample does not represent population)	Randomly sample <i>all</i> cohort members if possible
Data set selection bias (i.e., selection of studies may affect results)	Conduct meta-analysis of sensitivity of conclusions to studies. Use causal graph models to integrate diverse data sets.
Health status confounding, hospital admission/referral bias	<ul style="list-style-type: none"> <li>• If possible, use prospective cohort design and population-based cases and controls (Choi and Noseworthy, 1992)</li> </ul>
Selective attrition/survival (e.g., if exposure affects attrition rates)	Use a well-specified cohort. "Include non-surviving subjects in the study through proxy interviews" (Choi and Noseworthy, 1992).
Differential follow-up loss	Compare counter-factual survival curves
Detection/surveillance bias	Match cases to controls (or exposed to unexposed subjects) based on cause of admission.
Membership bias (e.g., lifestyle bias, socioeconomic history)	<ul style="list-style-type: none"> <li>• In cohort studies, use multiple comparison cohorts.</li> <li>• Hard to control in case-control studies.</li> </ul>
Self-selection bias; Response/volunteer bias	Achieve response rate of at least 80% by repeated efforts. Compare respondents with sample of non-respondents
<b>Information Collection Biases</b>	
Intra-interviewer bias	Blind interviewers to study hypotheses, subject classifications
Inter-interviewer bias	Use same interviewer for study and comparison groups
Questionnaire bias	Mask study goals with dummy questions; avoid leading questions/response options
Diagnostic suspicion bias	Hard to prevent in case-control studies. In cohort studies, make diagnosis and exposure assessments blind to each other.
Exposure suspicion bias	

**Page 23, lines 40-41. “The authors indirectly validated the quantitative exposure estimates by determining whether or not increasing exposure led to increasing silicosis.”**

*Comment: Exposure estimates are not exposures.* The authors did not determine whether increasing exposure led to increasing silicosis. They only selected exposure estimates that were consistent with this pattern. (Since the cumulative exposure estimates included duration of exposure, it is expected that very long durations/large cumulative exposures will occur disproportionately often for patients with silicosis, even if the estimates of exposure are very inaccurate. Thus, this does not constitute “validation” of the silica-specific component of the exposure estimates.)

*Comment: The Steenland et al. model has not been validated.* The Steenland *et al.* model has not been used to make testable (potentially falsifiable) predictions that have then been tested and validated using data not used to make the predictions.

*Comment: Steenland et al, used a statistical model that always produces a positive exposure-response relation, no matter what the data show* (as long as its input and output variables are positive) – even if the raw data actually show no relation or a negative (protective) relation between exposure and response. Its prediction of a positive relation between silica exposure and lung cancer is therefore meaningless, and does not provide a suitable basis or POD for quantitative risk assessment.

To see the problem, suppose that we fit a statistical model of the form “ $Y = \beta X$ ” to *purely random* data, formed by sampling  $X$  values randomly (uniformly) between 0 and 1 and, independently, sampling  $Y$  values randomly (uniformly) between 0 and 1. Then it is easy to see that a least-squares estimate of  $\beta$  will be significantly positive, not because  $X$  has any true relation to  $Y$ , but because the model goes through (0, 0) and through a scatter plot of data points that are all above and to the right of (0, 0). Sloping upward is all that the regression line can do, given the model “ $Y = \beta X$ ”. (This is an example of a bias due solely to *model specification error*. If the alternative model “ $Y = 0.5 + \beta X$ ” were fit to the data instead, then the new least squares estimate of  $\beta$  would be 0.)

Steenland *et al.* have done something similar by fitting the model “ $Y = \beta X$ ” to their data set, where “ $Y$ ” is  $\ln RR$ , having almost all positive values (possibly due to biases such as those in Table 1), and  $X$  is estimated exposure, consisting entirely of positive values. This model *must* give a positive estimated value of  $\beta$ . But this is only a mathematical necessity, not an empirical finding; it is brought about by the use of a specific mathematical model form that guarantees this result. It does not necessarily tell us anything about the true relation (if any) between exposure and risk. (The linear model ( $RR = 1 + \beta X$ ) with positive  $X$  values and  $RR$  values greater than 1 suffers from a similar bias, of necessarily yielding a positive estimate of  $\beta$ .)

Figure 1: Scatter Plot of Steenland *et al.* (2001) Raw Data.

$X$  = median cumulative exposure to respirable silica ( $\text{mg}/\text{m}^3$ ), from Table 1 of Steenland *et al.*  
 $Y$  = SMR for lung cancer, from Table 2 of Steenland *et al.*

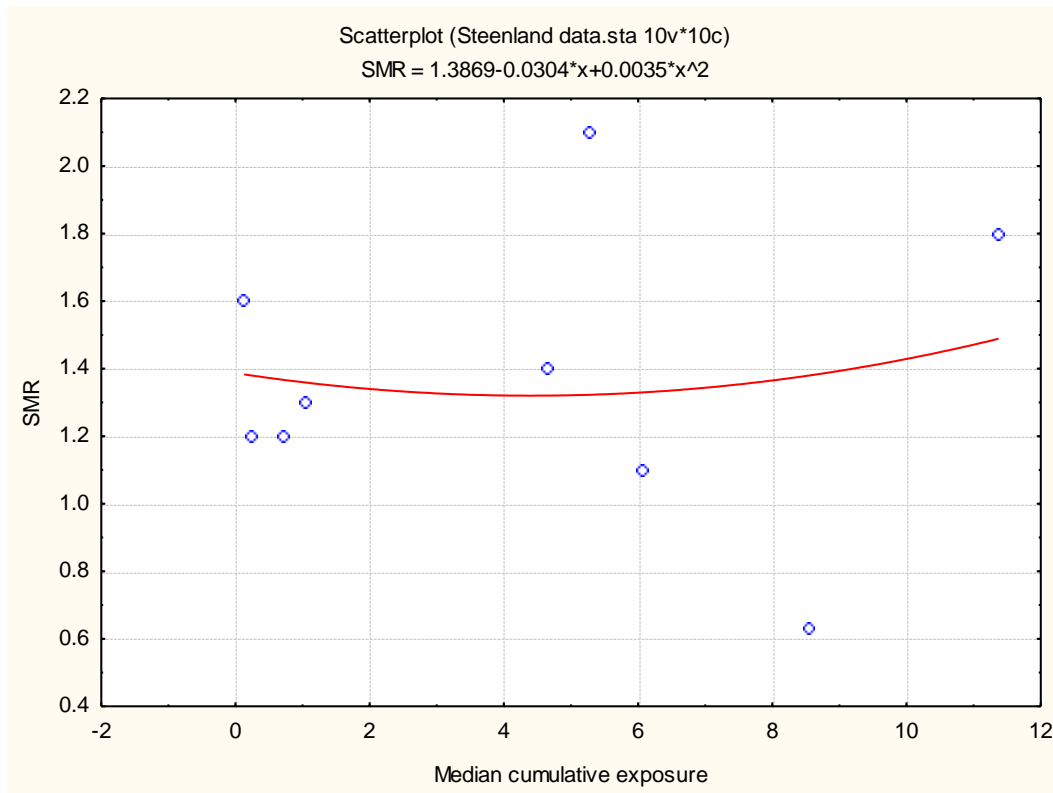


Figure 1 plots raw exposure and SMR values from the Steenland *et al.* paper, without any logarithmic transformations and without using a forced linear fit through the origin to artificially create a positive dose-response relation. Instead, the possibility of a nonlinear fit between  $X$  = median cumulative exposure and  $Y$  = SMR is allowed (by fitting a polynomial instead of a

forced straight line). If the true relation were linear through the origin, the model in Figure 1 could show that pattern. But that is not what the data show. Instead, *the raw data (exposure estimates and corresponding SMR estimates) show no positive relation at all between estimated exposure and lung cancer risk*, except possibly (non-significantly) at the highest estimated exposure levels. (See Figure 1 of Steenland *et al.* for a similar figure based on a spline curve analysis that does not impose the tight mathematical straightjacket used in their main analyses and conclusions. Interestingly, Steenland *et al.* refer to their spline model as showing a “monotonic increase in risk with increasing exposure,” but the curve in their figure appears to be initially declining.)

By selecting different model forms (e.g., logarithmic, exponential, polynomial, linear without intercept, linear with intercept, etc.), a modeler can obtain any regression-based relation he wants – positive, negative, or zero – between exposure and risk from these data. For example, to produce a negative (“protective”) relation between exposure and risk from the data in Figure 1, one could simply fit an exponential model; the best fit is:  $SMR = 1.3414 * \exp(-0.0065 * x)$ . In this model, larger average exposures to silica correspond to *reduced* risks of lung cancer. Steenland *et al.*, instead chose to fit a logarithmic model with no intercept, and thus obtained a positive rather than a negative relation; in their model, larger estimated exposure values correspond to larger estimated risks of lung cancer. Either model can be fit to the data, and the choice of a model completely determines the resulting statistical relation and conclusions.

Steenland *et al.* (2001, p. 780) concluded that “We found a positive monotonic exposure-response trend across quintiles of cumulative exposure.” They could equally well have fit a different model (e.g., the above exponential one) and found a *negative* monotonic exposure-response trend across quintiles of cumulative exposure. This is a good indicator that *the only valid conclusion that can be drawn is that the data set is ambiguous: apart from externally imposed modeling assumptions, it does not show any significant true relation between exposure and risk*. Any interpretation of the Steenland *et al.* data as supporting a positive (or negative, i.e., protective) causal relation between silica exposure and lung cancer risk is an artifact of modeling choices and preferences, not a valid implication of the data *per se*.

**Recommendation** Do not use the study of Steenland *et al.* (2001) as the key study, since its reported findings and conclusions are driven by unvalidated modeling assumptions, rather than by data.

*Recommendation:* Instead of the study of Steenland *et al.* (2001), use the larger and more recent studies reviewed by Pelucchi *et al.* (2006). Analyze the data using nonparametric or flexible statistical models, rather than using a model that imposes pre-determined conclusions on the data.

*Recommendation:* Recognize that the best current evidence is that silica exposure increases lung cancer risk only if there is sufficient exposure to cause silicosis.

***p. 24, lines 11-12. “The authors indicate that lung cancer was consistently related to silica exposure across all studies.”***

*Comment:* *There is no such consistent relation.* The authors chose an *ad hoc* mathematical model that implies this consistency – it is not present in the data (see Figure 1). Different choices of models would reverse this conclusion, as just discussed. (Also, actual silica exposures were not known, so it is not logically possible to claim that they are consistently related to lung cancer.) For the estimated exposures, the authors correctly noted the very large heterogeneity across studies. There is no consistent relation between silica exposure and lung cancer in these studies, apart from whatever consistency modelers may assume and impose on the data.

***Page 24, lines 12-14. “A log-linear multiplicative risk model was selected as the preferred model. The basis of this selection included the historical use of this model for human epidemiological data and the lack of a biological basis for selecting an alternative model.”***

*Comment:* *The selected model is not appropriate for lung cancer.* Biologically motivated models for lung cancer are available, and should be used instead. The “log linear multiplicative risk model” does not give a valid (or validated) description of the age-specific hazard rate for lung cancer as a function of exposure history. Other, equally valid (or invalid) models give very different conclusions. Rather than fitting more or less *ad hoc* statistical models to selected data, alternative models that have a biological basis and epidemiological support specifically for lung carcinogenesis should be used. Although the TS refers to a “lack of a biological basis for selecting an alternative model,” we believe that this is not justified. Both the two-stage clonal expansion (TSCE) model for exposure-dependent lung cancer risk, and the recently developed multistage clonal expansion model (MSCE) extension of the TSCE, provide useful, biologically

motivated, alternative models. (See Hazelton WD, Moolgavkar SH, Curtis SB, Zielinski JM, Ashmore JP, Krewski D. [Biologically based analysis of lung cancer incidence in a large Canadian occupational cohort with low-dose ionizing radiation exposure, and comparison with Japanese atomic bomb survivors](#). J Toxicol Environ Health A. 2006 Jun <sup>27</sup>; 69(11):1013-38; Cox LA Jr., [Could Removing Arsenic from Tobacco Smoke Significantly Reduce Smoker Risks of Lung Cancer?](#) *Risk Analysis* 2009. 29(1):3-17. <sup>28</sup>

*Recommendation:* Use a biologically based model appropriate for lung cancer, rather than continuing to use curve-fitting of statistical models that lack biological justification for lung cancer risks.

***Page 24, line 17. “The cumulative exposure metric fit the data well and was used in this assessment.”***

*Comment:* *The cumulative exposure metric does not fit the data well*, at least in any usual statistical sense. (It fits the data “successfully”, according to the criterion, discussed by Steenland *et al.*, of supporting their hypothesis of a monotonic increasing relation between estimated exposure and health risks. But support for a specified hypothesis or pattern is not the usual test of a “good” fit, and other metrics that do not support this hypothesis might fit the data much better, as suggested by the polynomial curve in Figure 1.) Figure 1 clearly shows that the cumulative exposure metric explains almost none of the variance in SMRs across studies; thus, by most usual statistical measures, it does *not* “fit the data well”.

*Recommendation:* Use statistical models and methods that explicitly model *measurement and estimation errors* for exposure intensities and durations, and that keep duration and intensity as separate explanatory variables. Use dosimetric models that allow different exposure intensities to have different potencies and that recognize that a high average exposure intensity may also be associated with relatively high peak exposures that could disproportionately contribute to risk. (Kriebel D, Checkoway H, Pearce N. [Exposure and dose modelling in occupational epidemiology](#). *Occup Environ Med*. 2007 Jul;64(7):492-8.)<sup>29</sup>

**Comments on TCEQ's Proposed Silica Development Support Document  
Crystalline Silica Panel  
American Chemistry Council**

January 30, 2009

**References**

1. B. A. Katsnelson and L. I. Privalova (1984), "Recruitment of phagocytizing cells into the respiratory tract as a response to the cytotoxic action of deposited particles", *Environ Health Perspect.*, 55: 313-325,  
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1568354>.
2. ITER Definitions, International Toxicity Estimates for Risk (ITER),  
<http://iter.ctcnet.net/publicurl/glossary.htm>
3. D.B. Warheit, T.A. McHugh, M.A. Hartsky (1991), "Differential pulmonary responses in rats inhaling crystalline, colloidal or amorphous silica dusts", *Scand J Work Environ Health*, 21 Suppl 2:19-21,  
[http://www.ncbi.nlm.nih.gov/pubmed/8929682?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/8929682?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
4. M. Maier (2001), "Amorphous Silica In Working Environments, A Toxicological Overview", Lecture at the "Silica 2001" in Mulhouse, France, [http://www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/ronlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological\\_Overview\\_Amorphous\\_Silica\\_in\\_Working\\_Environment.pdf](http://www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/ronlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological_Overview_Amorphous_Silica_in_Working_Environment.pdf).
5. J.L. Wright, M. Cosio, A. Churg (2008), "Animal models of chronic obstructive pulmonary disease", *Am J Physiol Lung Cell Mol Physiol.*, 295(1):L1-15,  
[http://www.ncbi.nlm.nih.gov/pubmed/18456796?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18456796?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
6. The South African Department of Labour (2009), "Silica exposure and its effect on the physiology of workers", <http://www.labour.gov.za/documents/useful-documents/occupational-health-and-safety/silica-exposure-and-its-effect-on-the-physiology-of-workers>
7. L.A. Cox, Jr., D.A. Popken (2007), "Some limitations of aggregate exposure metrics", *Risk Analysis*, 27(2):439-45,  
[http://www.ncbi.nlm.nih.gov/pubmed/17511710?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17511710?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

8. D.B. Warheit, M.C. Carakostas, D.P. Kelly, M.A. Hartsky (1991), "Four-week inhalation toxicity study with Ludox colloidal silica in rats: pulmonary cellular responses", *Fundam Appl Toxicol.* 16(3):590-601,  
[http://www.ncbi.nlm.nih.gov/pubmed/1649779?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/1649779?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
9. K.H. Kilburn (1984), Particles causing lung disease. *Environ Health Perspect.*, 55:97-109. <http://www.ehponline.org/members/1984/055/55009.PDF>,  
[http://www.ncbi.nlm.nih.gov/pubmed/6376114?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/6376114?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
10. Y. Chen, J. Chen, J. Dong, Y. Jin(2004), Comparing study of the effect of nanosized silicon dioxide and microsized silicon dioxide on fibrogenesis in rats, *Toxicol Ind Health*, 20(1-5):21-7,  
[http://www.ncbi.nlm.nih.gov/pubmed/15807405?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/15807405?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
11. P.A. Valberg and E.A. Crouch (1999), "Meta-analysis of rat lung tumors from lifetime inhalation of diesel exhaust", *Environ Health Perspect*, 107(9): 693–699,  
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1566471>
12. J.C. Pairon, P. Brochard, M.C. Jaurand, J. Bignon (1991), "Silica and lung cancer: a controversial issue", *Eur Respir J*, 4(6):730-44,  
[http://www.ncbi.nlm.nih.gov/pubmed/1653712?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/1653712?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
13. M. Maier (2001), "Amorphous Silica In Working Environments, A Toxicological Overview", Lecture at the "Silica 2001" in Mulhouse, France, [http://www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/rdonlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological\\_Overview\\_Amorphous\\_Silica\\_in\\_Working\\_Environment.pdf](http://www.degussa-nano.de/nano/MCMSbase/Pages/ProvideResource.aspx?respath=/NR/rdonlyres/1E02FAD4-E5D6-4CE2-8E5C-E19F4DAC7838/0/Toxicological_Overview_Amorphous_Silica_in_Working_Environment.pdf) .
14. K.H. Kilburn (1984), "Particles causing lung disease", *Environ Health Perspect.*, 55:97-109, p. 102, [www.ehponline.org/members/1984/055/55009.PDF](http://www.ehponline.org/members/1984/055/55009.PDF) ,  
[http://www.ncbi.nlm.nih.gov/pubmed/6376114?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/6376114?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
15. V. Jacob, P. Jacob (2004), "Modelling of carcinogenesis and low-dose hypersensitivity: an application to lung cancer incidence among atomic bomb survivors", *Radiat Environ Biophys.*, 42(4):265-73,  
[http://www.ncbi.nlm.nih.gov/pubmed/14676961?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/14676961?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)

16. W.D. Hazelton, S.H. Moolgavkar, S.B. Curtis, J.M. Zielinski, J.P. Ashmore, D. Krewski (2006), “Biologically based analysis of lung cancer incidence in a large Canadian occupational cohort with low-dose ionizing radiation exposure, and comparison with Japanese atomic bomb survivors”. *J Toxicol Environ Health A.*, 69(11):1013-38, [http://www.ncbi.nlm.nih.gov/pubmed/16840251?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/16840251?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
17. L.A. Cox, Jr. (2009), “Could Removing Arsenic from Tobacco Smoke Significantly Reduce Smoker Risks of Lung Cancer?”, *Risk Analysis*, 29(1):3-17, [http://www.ncbi.nlm.nih.gov/pubmed/19000069?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19000069?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
18. Department of Health and Human Services, Lung Cancer and Inflammation (RO1), <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-046.html>
19. Cancer Research UK, Lung Cancer risk factors, <http://info.cancerresearchuk.org/cancerstats/types/lung/riskfactors/>
20. National Institute for Occupational Safety and Health, 3.2d) Provision of Relevant Mechanistic and Dose-Response Data to Standard-Setting Bodies, <http://www.cdc.gov/niosh/nas/RDRP/ch3.2d.htm>
21. Lung cancer mortality among silicotic workers in Hong Kong—no evidence for a link, <http://annonc.oxfordjournals.org/cgi/content/full/18/6/1056>
22. *Int Arch Occup Environ Health*. 2008; <http://lib.bioinfo.pl/pmid:19066933>
23. Cancer Research UK, Lung Cancer risk factors, <http://info.cancerresearchuk.org/cancerstats/types/lung/riskfactors/>
24. NIOSH, 3.2d) Provision of Relevant Mechanistic and Dose-Response Data to Standard-Setting Bodies, <http://www.cdc.gov/niosh/nas/RDRP/ch3.2d.htm>
25. Z. Jin, *et al.* (2008), “Identification of differentially expressed genes in rat silicosis model by suppression subtractive hybridization analysis”, *Acta Biochim Biophys Sin.*, 40(8):740-6, [http://www.ncbi.nlm.nih.gov/pubmed/18685790?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/18685790?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
26. C. Pelucchi, E. Pira, G. Piolatto, M. Coggiola, P. Carta and C. La Vecchia (1996-2005), Occupational silica exposure and lung cancer risk: a review of epidemiological studies, <http://annonc.oxfordjournals.org/cgi/content/full/17/7/1039>

27. W.D. Hazelton, S.H. Moolgavkar, S.B. Curtis, J.M. Zielinski, J.P. Ashmore, D. Krewski (2006), "Biologically based analysis of lung cancer incidence in a large Canadian occupational cohort with low-dose ionizing radiation exposure, and comparison with Japanese atomic bomb survivors". *J Toxicol Environ Health A.*, 69(11):1013-38,  
[http://www.ncbi.nlm.nih.gov/pubmed/16840251?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/16840251?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
  
28. L.A. Cox, Jr. (2009), "Could Removing Arsenic from Tobacco Smoke Significantly Reduce Smoker Risks of Lung Cancer?", *Risk Analysis*, 29(1):3-17,  
[http://www.ncbi.nlm.nih.gov/pubmed/19000069?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/19000069?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
  
29. D. Kriebel, H. Checkoway, N. Pearce (2007), "Exposure and dose modelling in occupational epidemiology", *Occup Environ Med.*, 64(7):492-8.,  
[http://www.ncbi.nlm.nih.gov/pubmed/17582090?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed\\_ResultsPanel.Pubmed\\_DefaultReportPanel.Pubmed\\_RVDocSum](http://www.ncbi.nlm.nih.gov/pubmed/17582090?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)