Texas Commission on Environmental Quality Response to Public Comments Received on the April 2015 Proposed Vinyl Acetate Development Support Document

The public comment period for the April 2015 Proposed Development Support Document (DSD) for vinyl acetate ended in July 2015. The Toxicology Division (TD) received public comments from the Vinyl Acetate Council (VAC), a not for profit association, on July 17, 2015. The TD of the Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by the VAC to provide technical comments on the proposed DSD for vinyl acetate. 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 the comments from the VAC and TCEQ responses are provided below. The full comments and cover letter are provided in the Appendix. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

Comment 1:

VAC:

1. Page 6, Line 9

Issue: Difference between TCEQ's and NRC's Analysis of the Smyth and Carpenter study (1973)

The derivation of the Acute ReV is based on the Smyth and Carpenter human study where TCEQ has stated that the LOAEL is 20 ppm. TCEQ notes a similar assessment was prepared by the National Research Council for establishing Acute Exposure Guideline Levels (AEGL) for VAM, which relies on the same human study (Smyth and Carpenter, 1973).

The NRC analysis differed from TCEQ's by using an intrahuman uncertainty factor (UF) of 3 in contrast with TCEQ's factor of 10. NRC justified its 3-fold UF noting that irritation responses are not likely to vary significantly between individuals. Additionally, the NRC characterized the 20 ppm as a human NOAEL as compared to TCEQ, which identified the 20 ppm as a LOAEL. Further, the NRC stated the effects at 20 ppm, "are considered to be mild and below a notable discomfort threshold."

Recommendation: Given the recent NRC AEGL report, VAC recommends that TCEQ better explain its rationale for decisions that differ from NRC such as their choices of the point of departure and uncertainty factors.

TCEQ Response:

AEGLs are Public Emergency Response Guidelines that are intended for emergency exposure periods ranging from 10 minutes to 8 hours. The NRC guidelines state the AEGL-1 is an air concentration at which the general population, including sensitive subpopulations, could experience "notable discomfort, irritation, or certain asymptomatic, nonsensory effects." On the other hand, ESLs are set to protect human health and welfare, and concentrations at the ESL are

not likely to cause an adverse health effect in the general public, including sensitive subgroups such as children, the elderly, pregnant women, and people with preexisting health conditions. This difference in purpose inherently makes an ESL more protective and more conservative than an AEGL, and consequently lower PODs and higher UFs may be used in the derivation of ESLs. Therefore, the DSD was not revised in response to this comment.

Comment 2:

VAC:

2. Pg 10, Line 32

Issue: The quality of the TCEQ assessment would be enhanced if TCEQ did not rely on secondary sources of information when the published articles are readily available.

The TCEQ states that:

"Hurtt et al. (1995), as reported in NRC (2013), conducted developmental studies where confirmed-mated SD rats were exposed to VA concentrations of 0, 50, 200, or 1,000 ppm for 6 h/d from GD 6-15 and dams sacrificed on GD 20 (exposure method not described)."

Recommendation: The Hurtt et al. publication is readily available (copy attached). Here and elsewhere, TCEQ is encouraged to rely on the paper itself and not a secondary source review (e.g., NRC). While the bottom line conclusions will not change for the developmental study, the published paper provides additional details on the inhalation study that, if included, could enhance the quality and credibility of the review. It is further relevant to note that Hurtt et al. included both oral (drinking water) and inhalation routes of exposure.

TCEQ Response:

The TCEQ agrees that the use of primary data is preferred over using secondary sources. The original Hurtt et al. (1995) publication was reviewed and additional information was added to the DSD. Information regarding the drinking water study was also included.

Comment 3:

VAC:

3. Pg 11, Line 6

Issue: The discussion of mode of action should include greater attention to the potential role of acetaldehyde.

The MOA for irritation is stated to be unknown but may be due to cytotoxicity by intracellular acidification. While intracellular acidification may be the critical key event, it is possible that acetaldehyde, the reactive metabolite of VAM, also contributes to cytotoxicity by a variety of mechanisms. Sensory irritation, via vagal or other irritant receptors is also possible with VAM as the reported RD_{50} in mice is 380 ppm (1340 mg/m^3) (reported by Dudek et al., 1996).

Recommendation: Expand the discussion regarding the MOA to note that irritation could be due to acetic acid either alone or with the VAM metabolite acetaldehyde, or from irritant receptor stimulation. For example, it could be useful to add a short sentence at the end of the sentence on Page 11, line 7: "Acetaldehyde is a reactive aldehyde, produced naturally in the body and through metabolism of VAM. Acetaldehyde may also contribute to cytotoxicity and nasal irritation following VAM inhalation."

TCEQ Response:

The TCEQ appreciates the importance of the metabolite acetaldehyde in the cytotoxicity of VA. The text on mode of action (MOA) has been updated to make this clearer.

Comment 4:

VAC:

4. Pg 21, Line 11

Issue: This section correctly raises pH reduction as a potential primary cause of cytotoxicity in cells metabolizing VAM to acetaldehyde and acetic acid. Acetaldehyde is a reactive aldehyde and may also contribute to cytotoxicity where physiological levels are significantly exceeded. TCEQ should consider expanding its discussion on the role of acetaldehyde. We would also like to note that the VAC research program is producing new insights into the specific role acetaldehyde may play, and how dosimetry, tissue metabolism and pathology align and can be used to improve VAM risk assessment.

Recommendation: The TCEQ should consider revising the existing text on page 21, line 21. For example, immediately after the sentence detailing pH reduction as the first pharmacodynamic effect, add "acetaldehyde, when tissue levels significantly exceed physiological levels under conditions of high VAM exposure, may also contribute to cytotoxicity." Then, revise the following sentence to include acetaldehyde as another cytotoxic metabolite "Because acetaldehyde and acetic acid can both cause cytotoxicity, either directly, or through pH reduction, the tissue concentrations of these metabolites…."

Further, the TCEQ should consider incorporating a recent review of the genotoxicity of VAM and acetaldehyde (Albertini, Crit Rev Toxicology, 2013).

TCEQ Response:

The TCEQ appreciates the importance of the metabolite acetaldehyde in the cytotoxicity of VA. The text on MOA has been updated to make this clearer. A reference to the Albertini paper has been included.

Comment 5:

VAC:

5. Page 21, Line 26:

Issue: The TCEQ analysis describes several “flaws” in the PBPK model-based risk assessment of VAM published by Bogdanffy et al. (1999) as reasons for not using the PBPK model in their development of exposure standards for VAM. Several simple clarifications to the text would assure that the flaws attributed to the benchmark dose analysis (in that paper) are not confused with errors in the development or application of the PBPK model in the VAM risk assessment. For example, the issues raised by TCEQ are solely related to the benchmark dose (i.e., lumping endpoints, p-values) analysis element of the risk assessment. None are related to the application of the PBPK model.

Recommendation: TCEQ should consider revising the text so it is clear that the flaws in the Bogdanffy et al. (1999) analysis are related only to the BMD analysis.

TCEQ Response:

The TCEQ agrees that the Bogdanffy et al. (1999) PBPK model is a well-developed and useful model in the review of VA toxicity. The TCEQ has altered the language in the DSD to better explain that the issues with the PBPK model that led to it not being used are differences in the TCEQ procedures rather than flaws in the actual model.

Comment 6:

VAC:

6. Page 21, Line 32 onward:

Issue: This section ends with a sentence that proposes that the similarity between the 47.1 ppm LED produced by Bogdanffy et al. (1999) and the 50 ppm used by TCEQ, supports the accuracy of 50 ppm point of departure (POD) chosen by the TCEQ. This sentence follows a presentation of specific flaws in the BMD analysis used by Bogdanffy et al. (1999) to produce the LED of 50 ppm. The logic here appears flawed.

Recommendation: The TCEQ consider revising the section to eliminate the conundrum of articulating flaws in the published approach, then using the product of the published approach to support their similar conclusions about the POD.

TCEQ Response:

Although the Bogdanffy et al. (1999) PBPK model was not used in this analysis due to differences in TCEQ’s guidelines on combined incidence data and BMD modeling results, it is noteworthy that the two methods of POD determination, one using a NOAEL and the other PBPK modeling, result in very similar PODs. The TCEQ has clarified that the aspects of the PBPK model that led to it not being used are differences in the TCEQ procedures rather than flaws in the actual model.

Comment 7:

VAC:

7. Page 22, Line 26:

Issue: The TCEQ derived chronic ReV is almost identical to the value that would result from the full biologically based risk assessment published by Bogdanffy et al. (1999) if Bogdanffy et al. had used a composite UF of 30, instead of 10. There is an opportunity here to expand the text minimally to point out the similarity in the values as bolstering that the overall risk assessment conclusion is robust against some differences in assumptions (e.g. DAF, UF, BMD analysis).

Recommendation: The TCEQ might consider noting in the text that the Chronic ReV published by Bogdanffy (1 ppm) would be 333 ppb VA if Bogdanffy had applied composite UF of 30 (TCEQ) instead of 10. That is, a full biologically based risk assessment based on intracellular pH, applying TCEQ-derived UF, would result in virtually the same number as TCEQ's analysis produces. Use of intracellular acetaldehyde instead would result in a chronic ReV ~4 times lower.

TCEQ Response:

The similarities between the Bogdanffy et al. (1999) analysis and the TCEQ's chronic ReV derivation stem from using similar PODs and DAFs, both of which are compared in the updated DSD.

Comment 8:

VAC:

8. Page 22, Line 20:

Issue: TCEQ's choice to use the default U.S. EPA DAF could be bolstered by comparison to the data-derived DAF produced through use of the PBPK model and published by Bogdanffy and co-workers (Bogdanffy et al., 1999). The acetaldehyde and pH based tissue dose metrics the TCEQ proposes as the most biologically appropriate have been produced using the rodent-human PBPK model and published (Bogdanffy et al., 1999). These dose-metrics could be used in the risk assessment to address rodent-human differences in nasal tissue-dosimetry in place of the EPA RGDR approach or discussed as alternatives.

Recommendation: The TCEQ should consider discussing how the default and PBPK model derived DAF compare. The PBPK model based DAF can be calculated from tables in Bogdanffy et al. (1999). For example, the pH dose metric values are ~1 (Table 3, divide rat tissue pH by the human tissue pH). The value for acetaldehyde tissue concentration dose metric is about 0.2 (Table 2, divide rat acetaldehyde tissues dose by human acetaldehyde tissue dose dose). For tissue vinyl acetate concentrations the DAF is also approximately 1 (Table 2). Placing this information in the TCEQ VAM document allows comparison of the simple RGDR values based on physicochemical properties to those derived from a much richer understanding of difference in rats and humans, i.e. regional air flows, tissue metabolism. This may bring additional confidence in the value of 1 used by TCEQ because it is similar to the value derived by PBPK modeling for pH as a dose metric and tissue VAM as a dose metric. It also gives a lower bound on the DAF (0.2) if tissue acetaldehyde concentration is instead believed to be the driving force for toxicity.

We note here, though, that the VAC's research program anticipates developing computational model that brings together full 3-dimensional representations of the anatomy, and biochemistry (metabolism of VAM and acetaldehyde) of the rat nose and human nose. Using super computers, VAM containing air is "flowed" through the nose and tissue doses of VAM and acetaldehyde are calculated for all location in the nose. These regional doses will be mapped over the exact locations where early tissue damage occurs and tumors arise, to quantify the relationship between tissue dose and response for acetaldehyde. These analyses may improve upon the tissue acetaldehyde based tissue dose metrics produced by the earlier model used in the Bogdanffy et al. risk assessment for VAM (Bogdanffy, 1999).

TCEQ Response:

The TCEQ appreciates this detailed description of the Bogdanffy et al. (1999) model-based DAFs that are available. The DSD has been updated to compare these available values.

Comment 9:

VAC:

9. Pg. 28, Line 1

Issue: The cancer MOA may not solely be dependent upon intracellular acidification as the key pharmacokinetic step. For instance, cytotoxicity secondary to disruption of normal biological function resulting from protein alkylation and crosslinking of DNA and DNA to protein may contribute to regenerative repair, producing proliferative response in nasal mucosal epithelium at high level exposure of VAM. Further, the amount and timing of cell proliferation is likely to differ between olfactory and respiratory epithelium, as are the dose responses for acetaldehyde mediated adduct/DNA-protein crosslinks.

Recommendation: TCEQ may wish to consider incorporating the results from the VAC's research program.

TCEQ Response:

The TCEQ acknowledges the complexities of VA's threshold MOA. The DSD was updated to better clarify this complexity. However, since the MOA for the chronic noncarcinogenic potential is very similar to that of the carcinogenic potential, a detailed MOA description can also be found in the noncarcinogenic section.

Appendix – Cover letter and comments received from the Vinyl Acetate Council (VAC) on July 17, 2015.

VINYL ACETATE COUNCIL

1250 Connecticut Avenue, NW • Suite 700 • Washington, DC 20036
Phone: 202-419-1500 • Email: info@vinylacetate.org

July 17, 2015

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

Dear Sir or Madam:

On behalf of the Vinyl Acetate Council (VAC), I am pleased to submit the following comments on the Draft TCEQ Development Support Documents (DSD) for Vinyl Acetate Monomer (VAM) dated April 2015. The VAC is a not for profit 501(c)(6) association whose mission is to:

- collect and disseminate health, safety, and environmental information relevant to vinyl acetate;
- assess the need for additional information and sponsor studies accordingly;
- promote product stewardship with members and downstream users of vinyl acetate;
- monitor and participate in regulatory and other governmental proceedings to impact the safe and continued use of vinyl acetate; and,
- work with industry as well as government agencies in order to protect workers and consumers from exposure to VAM and VAM based products.

Members of the VAC are the major North American manufacturers of vinyl acetate monomer (VAM) as well as major producers of VAM-based polymers. As several VAC members have facilities in Texas, the DSD for VAM is of particular interest.

In general, the VAC is supportive of the DSD, which provides a comprehensive review of the literature relevant to establishing short and long-term Effect Screening Levels (ESLs) for VAM. VAC supports the position expressed in the DSD that VAM's tumorigenesis has a threshold-based mode of action (MOA). We suggest TCEQ consider bolstering its position by citing other research/regulatory agencies in North America and other parts of the world that have reached similar conclusions. Notable reviews include:

- 2008 EU Risk Assessment Report, http://echa.europa.eu/documents/10162/6434698/orats_summary_vinylacetate_en.pdf

- 2011 ECHA Committee for Risk Assessment, http://echa.europa.eu/documents/10162/13641/adopted_opinion_vinyl_acetate_en.pdf

- Health Canada assessment, http://www.ec.gc.ca/ese-ees/E41E17F4-59C5-44CC-94F3-155CE6094238/batch2_108-05-4_en.pdf

- EU SCHER, http://ec.europa.eu/health/archive/ph_risk/committees/04_scher/docs/scher_o_108.pdf

We believe that the justification for the presented threshold MOA can be further strengthened by incorporating recently completed and soon-to-be-available, research projects that the VAC is sponsoring. These research projects are designed to explain the role of VAM metabolism in the sequence of events leading to tumorigenesis, and characterize species differences in metabolism and nasal cavity anatomy for direct application in risk assessment (e.g., derivation of Dosimetric Adjustment Factors (DAF)). In addition to these general comments, we provide in the attached several specific issues/comments that we encourage TCEQ to consider in revising the DSD.

VAC is pleased to have had the opportunity to provide comments. Please feel free to contact me if you have any questions.

Sincerely yours,

Robert J. Fensterheim MPH
Vinyl Acetate Council

ATTACHMENT

Specific Comments on TCEQ Development Support Documents (DSD) for Vinyl Acetate (April 2015)

1. Page 6, Line 9
Issue: Difference between TCEQ's and NRC's Analysis of the Smyth and Carpenter study (1972)

The derivation of the Acute ReV is based on the Smyth and Carpenter human study where TCEQ has stated that the LOAEL is 20 ppm. TCEQ notes a similar assessment was prepared by the National Research Council for establishing Acute Exposure Guideline Levels (AEGL) for VAM, which relies on the same human study (Smyth and Carpenter, 1973).

The NRC analysis differed from TCEQ's by using an intrahuman uncertainty factor (UF) of 3 in contrast with TCEQ's factor of 10. NRC justified its 3-fold UF noting that irritation responses are not likely to vary significantly between individuals. Additionally, the NRC characterized the 20 ppm as a human NOAEL as compared to TCEQ, which identified the 20 ppm as a LOAEL. Further, the NRC stated the effects at 20 ppm, "are considered to be mild and below a notable discomfort threshold."

Recommendation:
Given the recent NRC AEGL report, VAC recommends that TCEQ better explain its rationale for decisions that differ from NRC such as their choices of the point of departure and uncertainty factors.

2. Pg 10, Line 32
Issue: The quality of the TCEQ assessment would be enhanced if TCEQ did not rely on secondary sources of information when the published articles are readily available.

The TCEQ states that:

> "Hurtt et al. (1995), as reported in NRC (2013), conducted developmental studies where confirmed-mated SD rats were exposed to VA concentrations of 0, 50, 200, or 1,000 ppm for 6 h/d from GD 6-15 and dams sacrificed on GD 20 (exposure method not described)."

Recommendation:
The Hurtt et al. publication is readily available (copy attached). Here and elsewhere, TCEQ is encouraged to rely on the paper itself and not a secondary source review (e.g., NRC). While the bottom line conclusions will not change for the developmental study, the published paper provides additional details on the inhalation study that, if included, could enhance the quality and credibility of the review. It is further relevant to note that Hurtt et al. included both oral (drinking water) and inhalation routes of exposure.

3. Pg 11, Line 6
Issue: The discussion of mode of action should include greater attention to the potential role of acetaldehyde.

The MOA for irritation is stated to be unknown but may be due to cytotoxicity by intracellular acidification. While intracellular acidification may be the critical key event, it is possible that acetaldehyde, the reactive metabolite of VAM, also contributes to cytotoxicity by a variety of mechanisms. Sensory irritation, via vagal or other irritant receptors is also possible with VAM as the reported RD50 in mice is 380 ppm (1340 mg/m3) (reported by Dudek et al. 1996).

Recommendation:
Expand the discussion regarding the MOA to note that irritation could be due to acetic acid either alone or with the VAM metabolite acetaldehyde, or from irritant receptor stimulation. For example, it could be useful to add a short sentence at the end of the sentence on Page 11, line 7: "Acetaldehyde is a reactive aldehyde, produced naturally in the body and through metabolism of VAM. Acetaldehyde may also contribute to cytotoxicity and nasal irritation following VAM inhalation."

4. Pg 21, Line 11
Issue: This section correctly raises pH reduction as a potential primary cause of cytotoxicity in cells metabolizing VAM to acetaldehyde and acetic acid. Acetaldehyde is a reactive aldehyde and may also contribute to cytotoxicity where physiological levels are significantly exceeded. TCEQ should consider expanding its discussion on the role of acetaldehyde. We would also like to note that the VAC research program is producing new insights into the specific role acetaldehyde may play, and how dosimetry, tissue metabolism and pathology align and can be used to improve VAM risk assessment.

Recommendation
The TCEQ should consider revising the existing text on page 21, line 21. For example, immediately after the sentence detailing pH reduction as the first pharmacodynamic effect, add "acetaldehyde, when tissue levels significantly exceed physiological levels under conditions of high VAM exposure, may also contribute to cytotoxicity." Then, revise the following sentence to include acetaldehyde as another cytotoxic metabolite "Because acetaldehyde and acetic acid can both cause cytotoxicity, either directly, or through pH reduction, the tissue concentrations of these metabolites…."

Further, the TCEQ should consider incorporating a recent review of the genotoxicity of VAM and acetaldehyde (Albertini, Crit Rev Toxicology, 2013).

5. Page 21, Line 26:
Issue: The TCEQ analysis describes several "flaws" in the PBPK model-based risk assessment of VAM published by Bogdanffy et al. (1999) as reasons for not using the PBPK model in their development of exposure standards for VAM. Several simple clarifications to the text would assure that the flaws attributed to the benchmark dose analysis (in that paper) are not confused with errors in the development or application of

the PBPK model in the VAM risk assessment. For example, the issues raised by TCEQ are solely related to the benchmark dose (i.e., lumping endpoints, p-values) analysis element of the risk assessment. None are related to the application of the PBPK model.

Recommendation
TCEQ should consider revising the text so it is clear that the flaws in the Bogdanffy et al. (1999) analysis are related only to the BMD analysis.

6. Page 21, Line 32 onward:
Issue: This section ends with a sentence that proposes that the similarity between the 47.1 ppm LED produced by Bogdanffy et al. (1999) and the 50 ppm used by TCEQ, supports the accuracy of 50 ppm point of departure (POD) chosen by the TCEQ. This sentence follows a presentation of specific flaws in the BMD analysis used by Bogdanffy et al. (1999) to produce the LED of 50 ppm. The logic here appears flawed.

Recommendation
The TCEQ consider revising the section to eliminate the conundrum of articulating flaws in the published approach, then using the product of the published approach to support their similar conclusions about the POD.

7. Page 22, Line 26:
Issue: The TCEQ derived chronic ReV is almost identical to the value that would result from the full biologically based risk assessment published by Bogdanffy et al. (1999) if Bogdanffy et al. had used a composite UF of 30, instead of 10. There is an opportunity here to expand the text minimally to point out the similarity in the values as bolstering that the overall risk assessment conclusion is robust against some differences in assumptions (e.g. DAF, UF, BMD analysis).

Recommendation
The TCEQ might consider noting in the text that the Chronic ReV published by Bogdanffy (1 ppm) would be 333 ppb VA if Bogdanffy had applied composite UF of 30 (TCEQ) instead of 10. That is, a full biologically based risk assessment based on intracellular pH, applying TCEQ-derived UF, would result in virtually the same number as TCEQ's analysis produces. Use of intracellular acetaldehyde instead would result in a chronic ReV ~4 times lower.

8. Page 22, Line 20:
Issue: TCEQ's choice to use the default U.S. EPA DAF could be bolstered by comparison to the data-derived DAF produced through use of the PBPK model and published by Bogdanffy and co-workers (Bogdanffy et al., 1999). The acetaldehyde and pH based tissue dose metrics the TCEQ proposes as the most biologically appropriate have been produced using the rodent-human PBPK model and published (Bogdanffy et al., 1999). These dose-metrics could be used in the risk assessment to address rodent-human differences in nasal tissue-dosimetry in place of the EPA RGDR approach or discussed as alternatives.

Recommendation
The TCEQ should consider discussing how the default and PBPK model derived DAF compare. The PBPK model based DAF can be calculated from tables in Bogdanffy et al. (1999). For example, the pH dose metric values are ~1 (Table 3, divide rat tissue pH by the human tissue pH). The value for acetaldehyde tissue concentration dose metric is about 0.2 (Table 2, divide rat acetaldehyde tissues dose by human acetaldehyde tissue dose dose). For tissue vinyl acetate concentrations the DAF is also approximately 1 (Table 2). Placing this information in the TCEQ VAM document allows comparison of the simple RGDR values based on physicochemical properties to those derived from a much richer understanding of difference in rats and humans, i.e. regional air flows, tissue metabolism. This may bring additional confidence in the value of 1 used by TCEQ because it is similar to the value derived by PBPK modeling for pH as a dose metric and tissue VAM as a dose metric. It also gives a lower bound on the DAF (0.2) if tissue acetaldehyde concentration is instead believed to be the driving force for toxicity.

We note here, though, that the VAC's research program anticipates developing computational model that brings together full 3-dimensional representations of the anatomy, and biochemistry (metabolism of VAM and acetaldehyde) of the rat nose and human nose. Using super computers, VAM containing air is "flowed" through the nose and tissue doses of VAM and acetaldehyde are calculated for all location in the nose. These regional doses will be mapped over the exact locations where early tissue damage occurs and tumors arise, to quantify the relationship between tissue dose and response for acetaldehyde. These analyses may improve upon the tissue acetaldehyde based tissue dose metrics produced by the earlier model used in the Bogdanffy et al. risk assessment for VAM (Bogdanffy, 1999).

9. Pg. 28, Line 1
Issue: The cancer MOA may not solely be dependent upon intracellular acidification as the key pharmacokinetic step. For instance, cytotoxicity secondary to disruption of normal biological function resulting from protein alkylation and crosslinking of DNA and DNA to protein may contribute to regenerative repair, producing proliferative response in nasal mucosal epithelium at high level exposure of VAM. Further, the amount and timing of cell proliferation is likely to differ between olfactory and respiratory epithelium, as are the dose responses for acetaldehyde mediated adduct/DNA-protein crosslinks.

Recommendation:
TCEQ may wish to consider incorporating the results from the VAC's research program.