Texas Commission on Environmental Quality (TCEQ)

Responses to Public Comments on the

Proposed Development Support Document for

4-Vinylcyclohexene

June 30, 2011

The public comment period for the proposed Development Support Document (DSD) for 4-vinylcyclohexene (VCH) ended in May 2011. ISP Elastomers (ISP) submitted comments. The Toxicology Division (TD) of the TCEQ appreciates the effort put forth by ISP to provide technical comments on the proposed DSD for VCH. 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 submitted by ISP is provided below, followed by TCEQ responses. The full comments of ISP are in Appendix 1. 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.

ISP Elastomers Comments Regarding the VCH DSD

Comment #1:

It is unclear to ISP why TCEQ chose an UF_D of 10 given the toxicity and mode-of-action (MOA) studies available on VCH and/or it metabolites. Instead, we believe that an UF_D of 1 is warranted for the following reasons: (1) the number of animals used and survived to study termination in the key study is sufficient for the hazard and dose-response assessment for deriving chronic ReVs . . . . (2) Additional information on the MOA for lethargy and tremors/lethality in mice should not be considered necessary . . . (3) There is sufficient information available to evaluate the reproductive and developmental toxicity potential of VCH . . .

Response #1:

The UF_D of 10 was not reduced to 1 as suggested by ISP, but was reduced to a value of 6 for the chronic database, based on comments received from ISP. The DSD was revised to include the following justification for an UF_D of 6:

A UF_D of 6 was used. A 13-wk inhalation study in rats and mice were available but the highest concentration tested, which was the LOAEL, was well above the maximum tolerated concentration. Although a two-generation oral gavage reproductive study in mice did not indicate reproductive effects (Grizzle et al. 1994), inhalation studies investigating two-generation reproductive effects as well as inhalation developmental studies are not available. Confidence in the database is medium.

Comment #2:

Page 5, line 2. The two-day micronucleus study was conducted for the U.S. EPA, not for E.I. DuPont Nemours & Co…

Response #2:

The DSD has been revised to remove the statement that the micronucleus study was conducted for E.I. DuPont Nemours & Co.

Comment #3:

Page 10 (Section 3.1.5, lines 4-11). The use of an UF_D of 10 for the acute ReV is unwarranted…

Response #3:

The UF_D of 10 was reduced to a UF_D of 6 based on a review of the acute database. The reason the UF_D was set at 6 was the 2-day and 2-wk inhalation studies did not examine a wide range of toxicity endpoints after inhalation exposure to VCH and short-term developmental studies that examined a wide range of developmental effects were not available. The oral gavage chronic reproductive study is not sufficient to investigate potential developmental effects. The DSD has been revised as follows:

Two-day and 2-wk inhalation studies in rats and mice were available but these studies did not examine a wide range of toxicity endpoints after inhalation exposure to VCH, although oral gavage studies provide additional data on endpoints that were not evaluated in the inhalation studies. An oral gavage chronic reproductive study in mice indicated that VCH does not significantly affect reproductive capability and does not appear to be fetotoxic or teratogenic. However, short-term inhalation developmental studies that examined a wide range of developmental effects were not available. Therefore, a UF_D of 6 was used. The confidence in the acute database is medium.

APPENDIX 1

ISP Elastomers Comments on TCEQ's Proposed Developmental Support Document for 4-Vinylcyclohexene dated January 2011

ISP ELASTOMERS

1615 Main Street • PO Box 667 • Port Neches, TX 77651 • Tel: 409-722-8321

May 2, 2011

TCEQ Toxicology Section
MC-168, P.O. Box 13087
Austin, Texas 78711-3087

Re: Proposed DSD for 4-Vinylcyclohexane

To Whom It May Concern:

Pursuant to TCEQ's January 31, 2011 solicitation for public comment, ISP Elastomers, L.P. (ISP) is pleased to submit the attached comments on TCEQ's proposed Decision Support Document (DSD) for 4-vinylcyclohexane (VCH). ISP commends TCEQ's efforts to refine its approach to the development and application of ESLs, ReVs, and URFs, especially with regards to its outreach to the public and the regulated community.

ISP owns and operates two manufacturing facilities in Texas that operate under authority of various New Source Review (NSR) air quality permits. ESLs routinely play an important role in the NSR permitting for our sites in that they are one of the tools used by TCEQ to ensure that ISP's plants are operated in a manner that is protective of human health and the environment. Accordingly, ISP has kept abreast of TCEQ's efforts regarding VCH and offers the attached comments for TCEQ's consideration when finalizing the DSD.

ISP's specific comments that are provided in Attachment 1 deal with our belief that a UF_D of 1 rather than a UF_D of 10 should have been used to derive both the chronic and acute ReVs for reasons that can be summarized as follows:

- The testing procedures, including the number of animals used and survived in the key study, are sufficient for derivation of the chronic ReV and support a UF_D of 1.
- ISP believes that lethargy/tremors/lethality was properly addressed as a systemic effect in the key study and does not agree with the conclusion in the DSD that additional information for the MOA for lethargy and tremors/lethality is needed.
- ISP believes that the NTP continuous breeding study used to evaluate the reproductive and developmental toxicity potential of VCH was robust and does not agree with the conclusion in the DSD that an additional two-generation study is needed.
- ISP also believes that data from the same continuous breeding study are sufficient for the purpose of hazard assessment and support a UF_D of 1 for derivation of the acute ReV.

ISP appreciates TCEQ providing the opportunity to comment on this important initiative and we look forward to future dialogue on these matters.

Sincerely,

ISP ELASTOMERS, L.P.

Ronald E. Smith, CSP

Ron Smith
Environmental Manager
PO Box 667
Port Neches, TX 77651

International Specialty Products (ISP) submits the following comments to the Texas Commission of Environmental Quality (TCEQ) on the proposed 4-Vinylcyclohexene (VCH) Development Support Document (DSD). Chronic ReVs were derived from critical effects (lethargy/tremors/lethality and ovarian atrophy) seen in mice exposed to 1000 ppm VCH in a 13-week inhalation study (Bevan et al., 1996; Stadler, 1994), with a NOAEL of 250 ppm and a POD_{HEC} of 44.64 ppm. Uncertainty factors (UF) were applied which included an uncertainty factor of 10 for an incomplete database (UF_D).

It is unclear to ISP why TCEQ chose an UF_D of 10 given the toxicity and mode-of-action (MOA) studies available on VCH and/or it metabolites. Instead, we believe that an UF_D of 1 is warranted for the following reasons:

1. The number of animals used and survived to study termination in the key study is sufficient for the hazard and dose-response assessment for deriving chronic ReVs. The 13-week mouse inhalation toxicity study was conducted as part of a Testing Consent Order for VCH under Section 4(a) of the Toxic Substance Control Act. The studies were conducted according to the U.S. EPA testing guidelines 40CFR 798.2450 and under the U.S. EPA Good Laboratory Practice (GLP) Standards. The number of animals used in the 13-week mouse inhalation (10/sex/dose group) is the standardized sample size for subchronic toxicity guideline studies, and it was also sufficient in detecting adverse effects consistent with those seen in previously conducted oral gavage toxicity studies in mice. If no CNS effects/mortality and/or ovarian effects were observed in the 1000 ppm-exposed mice, then an UF_D of 10 might be warranted; however, these effects were seen in the 1000 ppm-exposed mice and the data show a clear LOAEL and NOAEL for deriving a chronic ReV with a high degree of confidence.

2. Additional information on the MOA for lethargy and tremors/lethality in mice should not be considered necessary (and thus an incomplete database when there is insufficient MOA information) for the derivation of the chronic ReV. The DSD states that "the MOA for lethargy and tremors/mortality is unknown, but appears to be due to CNS effects. Lethargy and tremor/mortality are considered to have a nonlinear MOA and be relevant to humans." The lethargy/tremors/lethality were considered as systemic effects and the dose metric used was the exposure concentration of the parent compound (VCH). This is a reasonable conclusion and approach based on the available information, and, as stated above, there is a clear NOAEL in the 13-week inhalation study. The DSD does not elaborate on what critical information would be needed from MOA studies that would result in a higher confidence in the chronic ReV.

3. There is sufficient information available to evaluate the reproductive and developmental toxicity potential of VCH. A continuous breeding protocol study (Grizzle et al., 1994) conducted by the oral route showed no adverse reproductive or fertility effects in two generations of mice at a maximum tolerated dose, even in the presence of ovarian toxicity. This study was conducted by the National Toxicology Program (NTP), and while there may be uncertainty in the extrapolation of dose-response data from the oral route to inhalation route, the results of the continuous breeding protocol study are sufficient for use on a qualitative basis for the purposes of hazard assessment. The

female mice in the 13-week inhalation study and the continuous breeding protocol study both showed ovarian toxicity. Therefore, the need for an additional two-generation reproductive toxicity study by the inhalation route is unwarranted. It is also unclear why TCEQ considers, "The confidence in the database investigating ovarian atrophy is low" given the number of toxicity and MOA studies that have been conducted on VCH (and/or its metabolites).

Other Comments

Page 5, line 2. The two-day micronucleus study was conducted for the U.S. EPA, not for E.I. DuPont Nemours & Co.

Page 10 (Section 3.1.5, lines 4-11). The use of an UF_D of 10 for the acute ReV is unwarranted. The DSD states that, "short-term inhalation reproductive/developmental studies that examined a wide range of developmental effects were not available" even though, "oral gavage studies provide additional data on endpoints that were not evaluated in the inhalation studies." As noted above in the discussion about the chronic ReV, the oral gavage continuous breeding protocol study conducted on VCH by the NTP (Grizzle et al, 1994) is sufficient for the purpose of hazard assessment and thus the database on VCH should be considered adequate for deriving an acute ReV.

References

Bevan, C., Stadler, J.C., Elliott, G.S., Frame, S.R., Baldwin, J.K., Leung, H.-W., Moran, E., and Panepinto, A.S. (1996) Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation exposure. Fundam. Appl. Toxicol. 32: 1-10.

Grizzle, T.B., George, J.D., Fail, P.A., Seely, J.C., and Heindel, J.J. (1994) Reproductive effects of 4-vinylcyclohexene in Swiss mice assessed by a continuous breeding protocol. Fundam. Appl. Toxicol. 22: 122-129.

Stadler, J. C. (1994) Subchronic Toxicity Study by the Inhalation Route in Rats and Mice with 4- Vinylcyclohexene. Conducted by Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Company, Haskell Laboratory Report No. 442- 93.