Texas Commission on Environmental Quality Response to Public Comments Received on the May 16, 2013 Proposed Acetone Development Support Document

The public comment period for the May 2013 Proposed Development Support Document (DSD) for acetone ended in August 2013. The Toxicology Division (TD) received public comments from (1) The Global Acetate Manufacturer's Association (GAMA), and (2) Dr. Michael Stark; both comments were submitted on August 12, 2013. The TD of the Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by GAMA and Dr. Michael Stark to provide technical comments on the proposed DSD for acetone. 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 GAMA and Dr. Michael Stark is provided below, followed by TCEQ responses. The full comments are provided in Appendix 1 (GAMA) and Appendix 2 (Dr. Michael Stark). Comments on issues that suggest changes in the DSD are addressed whereas comments agreeing with TCEQ's approach are not. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

The Global Acetate Manufacturer's Association (GAMA):

GAMA submitted information to the TCEQ concerning studies on the potential effects of acetone exposure. However, the GAMA submission consisted of comments on the *American Conference of Governmental Industrial Hygienists Notice of Intended Change for Acetone (October 16, 2011)* and did not specifically address particular aspects/issues, sections, or decisions of TCEQ's draft acetone DSD. Therefore, as no DSD-specific comments were received, no detailed responses were prepared by the TCEQ. GAMA states, "We hope that the information from GAMA's comments to ACGIH will be useful to you when revising the proposed DSD for acetone. Thank you very much for considering our comments."

TCEQ Response*:*

The TCEQ appreciates the information submitted, although DSD-specific comments were not provided. The TCEQ gave serious consideration to the relevant information contained therein and indeed found GAMA's comments to ACGIH to be useful when considering potential revisions to the acetone DSD.

Dr. Michael Stark:

Comment No. 1:

lrritation

ln the proposed DSD the term "irritation" is broadly used for all aspect of irritancy, and those noticed minimal effects from self reporting questionnaires are assessed as adverse effects

(LOAEL), but these observations should more likely be described as odormediated annoyance, which are hardly adverse.
J. Arts and colleagues of the independent Dutch research institute TNO reviewed critically the literature about the irritancy of acetone and differentiated the effects from exposure in sensory (physiologically) irritation (as nasal pungency and eye irritation) and perceived (psychologically) irritation. Particularly the latter effect is influenced by the perceived odor intensity and biased by the perception, and reflect an olfactory and not a trigeminal nerve stimulation.

They concluded that symptom reporting is not suitable for establishing the irritation threshold of acetone, as this is sensitive to odor intensity, information bias and exposure history of the subjects. The studies of Nelson, Matsushita and Stewart were not considered in their evaluation due to missing or poor quality of data, respectively were not intended for the analysis of irritancy.[3]

ln a further paper J. Arts et al. used the examples of acetone besides formaldehyde, furfural and sulphur dioxide for the questions how subjectively measured sensory irritation thresholds can be used for setting exposure limits and defined minimal requirements for the study design.[4]

TCEQ Response:

Response: It is known and not unexpected that the perception of odor (e.g., intensity), information bias (e.g., about the consequences of exposure), and prior experience with a chemical (e.g., occupational exposure history appears to decrease sensitivity to odor and irritation) can have some influence on the self-reporting of symptoms. However, this alone does not allow for a definitive determination that self-reported irritation is entirely (or even more probably) due to odor perception (without any contribution from trigeminal nerve stimulation) when odors may be perceived (e.g., in a chamber study) or that such studies should be entirely discredited and dismissed out of hand as having no value in helping to establish the possible lower limits of air concentrations associated with irritation as part of a review of relevant literature. The TCEQ acknowledges that there are uncertainties associated with utilization of the key studies in the acetone DSD (e.g., potential low bias in the determination of irritation LOAELs).

Arts et al. (2002), a study upon which the comments would have us rely, suggests that based on a single study (per Table 3 of Arts et al. 2002), the sensory irritation for acetone appears to lie between 10,000 and 40,000 ppm. While irritation is often a relatively sensitive effect, as summarized by Arts et al. (2002, 2006), much more serious effects can occur within or even below this irritation concentration range: ten breaths (with a nose clip) of 6,000 or 8,000 ppm acetone lasting approximately 30 seconds were reported to cause nausea, suffocation, slight dizziness, and a strong desire to withdraw; decreased rat brain weight at 19,000 ppm for 8 weeks; unconsciousness, dizziness, unsteadiness, confusion, and headache have been reported at > 12,000 ppm for up to 4 h. Although there is uncertainty associated with controlled exposure studies of self-reported symptoms like those discussed in the acetone DSD (e.g., Stewart et al. 1975, Matsushita et al. 1969a,b), regulatory agencies tend to prefer to err on the side of conservatism in protecting public health and the most sensitive members of the public. This is a different consideration and duty than those for occupational exposures, the perspective from

which the comments are written, where occupational levels may not protect the most sensitive of the worker population.

Comment No. 2:

Neurobehavioral / Neuroloqical Effects

Two of manifold performance tests in the study by Dick et al. showed effects in the acetone exposed group (250 ppm) and were rated as statistically significant. These results were assigned in the SDS as an adverse effect level, which seems to be very doubtful, as these observations were not time correlated and more complex tasks in the tests did not showed differences.

TCEQ Response:

Response: These comments refer to statistically significant increases in response time ($p < 0.01$) and false alarm rate ($p < 0.001$). False alarm rate exhibited some time dependence with the same statistically significant increases at both 3-4 and 5-6 hours of exposure and a somewhat larger increase at 7-8 hour post exposure when blood acetone levels continued to be significantly elevated, with a similar temporal pattern being observed for response time (see Table 5 of Dick et al. 1989). In regard to the absence of statistically significant differences for more complex tasks, the determination of critical effect generally relies upon the first effect to occur as dose rises and does not require that other related (or at least potentially related) but more complex endpoints also occur and/or achieve statistical significance.

Comment No. 3:

The German MAK Commissions analysed in 1993 the human behavioral reactions to acetone. Their evaluation based mainly on the studies performed by lfADo (as A. Seeber et al.) which did not yield significant neurobehavioral effects at 1000 ppm in the experimental and in the field study. Former regarding studies (as Matsushita) were disregarded due to poor study design respectively the single findings of reduced performance at 250 ppm in Dick's study was regarded as influenced by other factors.

The TWA ("MAK-value") was set to 500 ppm to avoid effects on mood ("Befindlichkeitsstörungen") and irritation (comment: also this term was used in the understanding of irritancy or better unpleasantness and not as trigeminal sensory irritation). The English translation of this evaluation is attached to this letter, but is also available via the web-site of the MAKCommission[5 6]

TCEQ Response:

Response: Although occupational limits (e.g., the MAK values themselves) are generally not suitable for regulatory use in protecting the public at large, their background documentation and review/discussion of available studies are often useful. In its discussion of the Seeber et al. studies, the MAK document notes that complaints of mucosal irritation (e.g., eyes, nose) at 1,000 ppm were similar to those in Dick et al. and ratings of well-being were adversely affected and clearly exposure related. Thus, although not supportive of effects on performance parameters like

those reported in Dick et al., such information is used by MAK to conclude that "there are reproducible findings for effects on mood and irritation (like the mucosal irritation described in earlier studies) for exposures under 1000 ml/m^3" and that there are "weak, reversible reactions seen at 500 ml/m^3 in some, but not all persons…" This provides some support for TCEQ's points of departure for irritation and neurobehavioral effects which are generally within a factor of 2 of 500 ml/m^3: "…the lowest potential short-term threshold for irritation is perhaps around 250-300 ppm acetone, which is slightly higher than but supports the lowest potential LOAEL for neurobehavioral effects (227 ppm) from Dick et al. (1989)..." While the MAK document indicates that Matsushita et al. results below 500 ml/m^3 (ppm) cannot be "unqualifiedly accepted," the TCEQ only uses this study as a supporting one. The document acknowledges that Dick et al. meets current standards in design and evaluation, and then seems to fault the study for examining a wide array of performance parameters and only finding two statistically affected parameters which could be due to chance or the influence of "other factors" conceivably. However, this is generally the case in studies which evaluate a significant number of endpoints, which is usually considered a desirable study attribute. Given p values of < 0.01 and < 0.001 at multiple time points for the same two measures (i.e., response time, false alarm rate), the TCEQ does not have a serious concern about the number of performance measures tested (32), and "other factors" which are not defined but could affect the outcome of a study are difficult to rule out and remain a common uncertainty.

Comment No. 4:

In the chapter Chronic Evaluation / Neurological of the SDS the field study by T. Satoh and K. Omae was reviewed and an LOAEL of 375 ppm was defined. I would like to comment tthis study in a later submission (after the deadline), as I have to check in my folders the initial study report (Engl. translation of the Jap. original) for preparing the comment.
I consider the necessity, that the SDS for acetone should not use the lowest effect levels reported in any study, but should rely on the results of the most reliable and robust studies.
By that approach we might also avoid that in later evaluations the same biased results of elder studies will be used again (the AEGL Committee had unfortunately not revised their report on our regarding comments, but keeps still the interim status).

TCEQ Response:

Response: The TCEQ did not receive additional comments on the Satoh et al. study, and agrees that reliable and robust studies should generally be relied upon. However, where the database for a chemical is limited in some respect (e.g., almost exclusively relying on subjective reports of irritation), the TCEQ may rely on toxicological studies with certain inherent uncertainties. In the face of uncertainty, regulatory agencies often err on the side of conservatism in the protection of public health and the most sensitive members of the public. This is a different consideration and duty than those for occupational exposures, as occupational levels may not protect the most sensitive of the worker population.

Comment No. 5:

Therefore I ask the experts of TCEQ to revise and modify their draft:

- in the chapter irritation the term "irritation" should be differentiated and specified, the reported symptoms should be checked for their relevance and adversity - by considering the analyses by TNO (J. Arts et al.);

TCEQ Response:

See the first response above.

Comment No. 6:

- additionally further regarding studies needs to be included (l miss here particularly the groundbreaking findings by Monell institute (P. Dalton et al.);

- in the neurobehavioral section the results of Dick's study should be more critically analysed and

- results of the IfADo-studies (Seeber et al.) needs to covered and compared.

TCEQ Response:

Additional limited information/discussion was included in the DSD.

Comment No. 7:

Additionally I propose to include in chapter 2 the reference to a publication by H.B. Singh (NASA) et al. about sources and fate of acetone in the ambient environment covering also an estimation of emissions from natural and biogenic sources which is missing in the earlier ATSDR document. [7]

TCEQ Response:

This reference has been added to the DSD.

Comment No. 8:

I hope my comments and remarks are helpful for the revision of the draft.

I will appreciate to answer any question or to provide any support.

TCEQ Response:

The TCEQ appreciates your thoughtful comments.

APPENDIX 1

Global Acetate Manufacturers Association (GAMA)

Comments Regarding the TCEQ Development Support Document for Acetone

GLOBAL
ACETATE
MANUFACTURERS'
ASSOCIATION

GAMA Headquarters
355, Lexington Avenue, 15th Floor
New York, NY 10017
U.S.A

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

12 August, 2013

Re: Comments on Development Support Document "Acetone" (Proposed, May 2013).

I am writing to you on behalf of the Global Acetate Manufacturers Association (GAMA). GAMA is the global association representing cellulose acetate manufacturers with members in Asia, Europe and the US. For more information on GAMA's members, please visit GAMA's website on: http://www.acetateweb.com/membership.htm. The organization was established to enhance the long-term viability of cellulose acetate and its derivative products on a worldwide basis. GAMA's mission is to advance, develop and promote these products, and to jointly address technical and policy issues faced by the industry.

Our member companies have over 50 years of experience with the use of acetone in an occupational setting and have extensive experience and knowledge of the hazards associated with this volatile solvent. In fact, many of the most important studies on the health effects of acetone have involved workers at our manufacturing sites. Likewise, we have sponsored numerous clinical studies aimed at distinguishing odor detection and awareness from the many purported irritative effects of acetone. Our detailed evaluation of the information contained in these toxicity studies from both laboratory animals and human volunteers show that acetone can be used safely and without health concern at the occupational exposure limits currently in place.

Because GAMA has been involved with acetone as a raw material for many years, we would like to share some of our expertise and information on acetone which may be of benefit to you in the Proposed Development Support Document (DSD) process. GAMA has been consistently monitoring the progress of the American Conference of Industrial Hygienists (ACGIH) review of Acetone under their "Notice of Intended Change" (NIC) process. We believe that the information we have shared with ACGIH would be of relevance in the Proposed DSD for acetone.

We have shared our comments with ACGIH on two occasions in 2011 and 2013, as we strongly disagree with ACGIH's proposal to lower the TLV value for acetone from 500 to 200 ppm. The first occasion was in July 2011 where GAMA submitted comments on the proposed reduction of the TLV value for acetone from 500 to 200 ppm based on the minimization of potential central nervous system effects. We contracted with Dr. David Morgott to analyze the draft of ACGIH's "Notice of Intended Change" Acetone document (11/05/2010) – please see attachment 1. As ACGIH's Chemical Substances Committee did not have time enough to discuss the TLVs in 2012, they published a second draft in 2013. For this second occasion, GAMA contracted with John O'Donoghue VMD, PhD, DABT. Dr. O'Donoghue has substantial toxicological experience, with specific experience around acetone, and he has reviewed the existing literature on acetone – please see attachment 2. This review demonstrates that there is clearly no support in the current available literature for ACGIH's proposal to reduce the TLV for acetone.

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GAMA is a not-for-profit entity incorporated in the State of Delaware, United States of America (Section 501(c) (6) of Delaware General Corporation Law)

We hope that the information from GAMA's comments to ACGIH will be useful to you when revising the proposed DSD for acetone. Thank you very much for considering our comments. Should you have any questions, please do not hesitate to contact us.

Best regards,

Dani Kolb
General Manager

Attachments:

1) Comments to the NIC Acetone TLV Documentation (11/05/2010)
2) Comments to the NIC Acetone TLV Documentation (01/02/2013)

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GAMA is a not-for-profit entity incorporated in the State of Delaware, United States of America (Section 501(c) (6) of Delaware General Corporation Law)

APPENDIX 2

Dr. Michael Stark

Comments Regarding the TCEQ Development Support Document for Acetone

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12. Aug. 2013

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ACETONE – Delevopment Support Document Proposed, May 2013

Dear Sirs,

I became just recently aware of this proposed DSD for acetone and like to comment it shortly and on short notice, as the chapters about irritation and neurobehavioral/neurotoxic effects contain elder, doubtful and biased studies respectively overestimate observations, but newer and improved studies with acetone are missing.

In my former position as Product Steward for the man-made fibre company Rhodia Acetow[1] which uses acetone as solvent in the spinning of acetate fibres, I followed the discussion about Aceton's toxicity. And I was particularly interested for neurological effects, irritation and and subjective symptoms after the "Institut für Arbeitsforschung an der Technischen Universität Dortmund" (IfADo)[2] wanted to perform a field study with our employees exposed to acetone in order to compare the results with their laboratory (exposure chambers) studies.

Irritation

In the proposed DSD the term "irritation" is broadly used for all aspect of irritancy, and those noticed minimal effects from self reporting questionnaires are assessed as adverse effects (LOAEL), but these observations should more likely be described as odormediated annoyance, which are hardly adverse.

J. Arts and colleagues of the independent Dutch research institute TNO reviewed critically the literature about the irritancy of acetone and differentiated the effects from exposure in sensory (physiologically) irritation (as nasal pungency and eye irritation) and perceived (psychologically) irritation. Particularly the latter effect is influenced by the perceived odor intensity and biased by the perception, and reflect an olfactory and not a trigeminal nerve stimulation.
They concluded that symptom reporting is not suitable for establishing the irritation threshold

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[1] Former company's name: Rhône-Poulenc Rhodia; current name: Solvay Acetow; located in Freiburg, Germany with sites in Brazil, France, Russia and U.S.A. (Kingsport, TN)

[2] Leibniz Research Centre for working Environment and Human Factors, the official German WHO Centre for Occupational Health: www.ifado.de

of acetone, as this is sensitive to odor intensity, information bias and exposure history of the subjects. The studies of Nelson, Matsushita and Stewart were not considered in their evaluation due to missing or poor quality of data, respectively were not intended for the analysis of irritancy.[3]

In a further paper J. Arts et al. used the examples of acetone besides formaldehyde, furfural and sulphur dioxide for the questions how subjectively measured sensory irritation thresholds can be used for setting exposure limits and defined minimal requirements for the study design.[4]

Neurobehavioral / Neurological Effects

Two of manifold performance tests in the study by Dick et al. showed effects in the acetone exposed group (250 ppm) and were rated as statistically significant. These results were assigned in the SDS as an adverse effect level, which seems to be very doubtful, as these observations were not time correlated and more complex tasks in the tests did not showed differences.

The German MAK Commission[5] analysed in 1993 the human behavioral reactions to acetone. Their evaluation based mainly on the studies performed by IfADo (as A. Seeber et al.) which did not yield significant neurobehavioral effects at 1000 ppm in the experimental and in the field study. Former regarding studies (as Matsushita) were disregarded due to poor study design respectively the single findings of reduced performance at 250 ppm in Dick's study was regarded as influenced by other factors.
The TWA ("MAK-value") was set to 500 ppm to avoid effects on mood ("Befindlichkeits-störungen") and irritation (comment: also this term was used in the understanding of irritancy or better unpleasantness and not as trigeminal sensory irritation). The English translation of this evaluation is attached to this letter, but is also available via the web-site of the MAK-Commission [5 6]

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I consider the necessity, that the SDS for acetone should not use the lowest effect levels reported in any study, but should rely on the results of the most reliable and robust studies. By that approach we might also avoid that in later evaluations the same biased results of

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[3] J.H.E. Arts et al.: "An analysis of human response to the irritancy of acetone vapors", Critical Reviews in Toxicology **32**, 43-66 (2002)

[4] J.H.E. Arts, C. deHeer and R.A. Woutersen: "Local effects in the respiratory tract: Development of subjectively measured irritation for setting occupational exposure limits", Int. Arch. Occup. Environ. Health **79**, 283-298 (2006)

[5] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area: http://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/index.html

[6] Remark: in this MAK-document an European CEC criteria document prepared by SCOEL (Scientific Expert Group on Occupational Exposure Limits) was mentioned, which proposed a TLV of 200 ppm; this document was revised in 1997 with a TLV of 500 ppm and can be found on the web site of DG Employment, Social Affairs & Inclusion of the European Commission
http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684

elder studies will be used again (the AEGL Committee had unfortunately not revised their report on our regarding comments, but keeps still the interim status).

Therefore I ask the experts of TCEQ to revise and modify their draft:
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- results of the IfADo-studies (Seeber et al.) needs to covered and compared.

Additionally I propose to include in chapter 2 the reference to a publication by H.B. Singh (NASA) et al. about sources and fate of acetone in the ambient environment covering also an estimation of emissions from natural and biogenic sources which is missing in the earlier ATSDR document. [7]

I hope my comments and remarks are helpful for the revision of the draft.

I will appreciate to answer any question or to provide any support.

Best regards

Michael Stark
Dr.rer.nat., Dipl.Chem., retired
(former position: Product Steward of Rhodia Acetow)

Attachment:
DFG [Deutsche Forschungsgemeinschaft]:Acetone. Nachtrag von 1993: The MAK-Collection Part 1: MAK Value Documentations (Editor: H. Greim), English translation (1996)
http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb6764e0007/pdf

[7] H.B. Singh et al.: „Acetone in the atmosphere: Distribution, sources, and sinks" J. Geophys. Res. **99**, 1805-1819 (1994); later publication of H.B. Singh with a working group at Harvard: D.J. Jacob et al. "Atmospheric budget of acetone" J. Geophys. Res. **107**, ACH 5-1 – ACH 5-19 (2002); *doi:10.1029/2001JD000694*