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American Chemistry Council
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February 28, 2005

Information Quality Guidelines Staff
US EPA - Room M1200
1300 Pennsylvania Ave., NW
Washington, DC 20008

RE: Request for Correction of the Isocyanates Profile pursuant to EPA's Information Quality Guidelines (IQG #04025)

Dear Information Quality Guidelines Staff:

On September 8, 2004, the American Chemistry Council Aliphatic Diisocyanates Panel (Panel) submitted a Request for Correction concerning the Isocyanates Profile posted by EPA on its Design for the Environment (DfE) website. On December 21, 2004, Susan B. Hazen of EPA sent a response to the Panel's request, explaining how the Agency would make changes in response to some of the Panel's points, and denying some other of the Panel's requests. Ms. Hazen's letter requested that, if the Panel chose to submit a Request for Reconsideration, it do so within 90 days of the update of the Webpage. That update was posted January 26, 2005.

The Panel first thanks EPA for its consideration of the Panel's Request for Correction, and for the changes EPA has made in response to that Request. The Panel believes that these changes improve the accuracy, quality and utility of the Isocyanates Profile.

With this letter, the Panel is requesting that EPA reconsider its denial of the request to revise statements concerning the relative toxicity of monomers and prepolymers. There is also an error in the information EPA has added that should be corrected.

Relative Toxicity of Monomer and Prepolymer

The Panel requested that the Profile be corrected to show that the evidence indicates prepolymers are significantly less toxic that the associated monomers. EPA's response disagrees with this request on the basis of industry product literature providing acute toxicity (4-hour LC_{50}) data for HDI monomer aerosols and HDI polyisocyanates.

However, the statement to which the Panel's request referred is in a section of the Profile titled, "Repeated Dose Respiratory Tract Toxicity." The statement itself is: "Based upon a very limited data set, it appears that diisocyanate prepolymers exhibit the same respiratory tract

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effects [as monomers] *in repeated dose studies*, but at slightly higher doses" (emphasis added).[1] As explained in detail in the Panel's Request for Correction, there are significant qualitative and quantitative differences between monomers and prepolymers in repeated dose studies. Based on no observed adverse effect levels in 90-day studies, there is approximately a 40-fold difference between the monomer and polyisocyanates of HDI.[2]

EPA's response indicates that the purpose of the Profile is to support the need for exposure reductions during spray applications of automotive coatings. Acute toxicity (LC_{50}) tests are designed to identify a concentration that is lethal over a short period of time. The lethality levels for the diisocyanates are far above any reasonably anticipated occupational exposure. In the context of automotive spray applications, the relevant concern is for respiratory effects from longer term, repeated exposures, and therefore the relevant animal data is that from repeated dose studies. The Profile appropriately discusses "Repeated Dose Respiratory Tract Toxicity," and the comparison of monomers and prepolymers should likewise be based on repeated dose toxicity data.[3]

The Panel therefore again requests that the Isocyanate Profile be corrected to state that the evidence indicates prepolymers are significantly less toxic than the associated monomers. An appropriate replacement for the current sentence in the Repeated Dose respiratory Tract Toxicity section and the Conclusion would be: "On the basis of repeated dose studies of HDI monomer and prepolymer, the prepolymer is significantly less toxic than the monomer."

Correction to the Amended Profile

In Appendix A-1 of the amended Profile, item (1) is headed, "Nomenclature provided by the American Chemical Council's Diisocyanates Panel." As accurately reflected in footnote 1 of Appendix A-1, the nomenclature was provided by the Aliphatic Diisocyanates Panel. This distinction is important because there is a separate Diisocyanates Panel within the American Chemistry Council which addresses different compounds than the Aliphatic Diisocyanates Panel.

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1 This sentence is repeated in the Conclusions section of the amended Profile.

2 The Panel's information on this issue is reproduced in the Appendix to this letter.

3 Even on the basis of acute toxicity data, it is not generally accurate that diisocyanates monomers and prepolymers have similar toxicity. As explained in the Panel's Request for Correction, large differences are seen in acute toxicity tests of IPDI monomer versus prepolymers, with the prepolymers showing much less toxicity. *See* Appendix to this letter.

If you have any questions, please call Sarah Loftus McLallen, Manager of the Aliphatic Diisocyanates Panel, at (703) 541-5607 or email her at Sarah_McLallen@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice-President, CHEMSTAR

cc: Clive Davies
Chief, Design for the
Environment Branch

Jamie Conrad
American Chemistry Council

APPENDIX

EXCERPT FROM SEPTEMBER 8, 2004 REQUEST FOR CORRECTION (IQR #04025)

C) Differences in Toxicity of the Monomer and Prepolymer. The Isocyanate Profile states: "Based upon a very limited data set, it appears that diisocyanate prepolymers exhibit the same respiratory tract effects in repeated dose studies [as monomers], but at slightly higher doses." To the contrary, there are both qualitative and quantitative differences between effects seen in studies of prepolymers versus monomers.

Qualitatively, observed differences between monomers and prepolymers in repeated dose studies may be a reflection of physical difference in the substances. The monomer for HDI is tested as vapor, whereas the prepolymer/polyisocyanates are tested as liquid aerosols. (This is because the vapor pressure of the polyisocyanates is low, such that even saturated vapor concentrations are insufficient to produces effects.) Due to the physical/chemical properties of the monomer (low water solubility, reactive), vapor exposures (monomer) tend to deposit in the nasal cavity of rats (which are obligate nasal breathers). Aerosolized material (polyisocyanate) primarily deposits in the deep lung. Thus, the lesions observed for tests of monomer vapor in rodents tend to be of the upper respiratory tract epithelium (hyperplasia, metaplasia, hyperkeratosis, olfactory cell degeneration, etc.), whereas the polyisocyanates tend to produce thickening of the pulmonary epithelium in the region of the terminal bronchioles/alveoli and occasionally produce pulmonary fibrosis in rats.

Quantitatively, significant differences are seen between monomers and prepolymers with respect to doses required to produce effects. A direct comparison of the toxicity of the monomer to the polyisocyanates can be made using studies with comparable designs. For HDI, the longest duration studies common to both the monomer and polyisocyanates are 90-day (subchronic) inhalation toxicity studies using rats. Mobay Inc. (1988) conducted a 90-day inhalation toxicity study of the monomer.[11] Pauluhn *et al.* (2001) recently published comparable studies of HDI polyisocyanates.[12]

For purposes of comparing these studies, the NOAEL was selected to assess differences in relative toxicity. The authors of the 90-day study of the monomer conclude that a NOEL was not established, but that the lowest concentration of 0.01 ppm is close to the threshold. This conclusion is supported by the results from the 1-year interim sacrifice groups from a chronic toxicity study (Mobay Inc., 1989).[13] At the 1-year interim period, a clear NOEL was reported at an exposure concentration of 0.005 ppm. Thus, a logical deduction would be that the NOAEL for the shorter-duration 90-day study would be no lower than 0.005 ppm (0.034 mg/m3). The NOAEL values for the 90-day studies of the polyisocyanates of HDI were in the range of 3-4 mg/m3. Therefore, it can be concluded that the polyisocyanates are substantially less toxic than the monomer of HDI. On a Total Reactive Isocyanate Group (TRIG) basis, the NOAELs were 0.017 mg TRIG/m3 of air for HDI monomer versus 0.71-0.73 mg TRIG/m3 of air for HDI polyisocyanate. Thus, there is approximately a 40-fold difference between the monomer and polyisocyanates of HDI on the basis of their respective NOAELs.

Repeated dose studies are not available for prepolymers of IPDI. However, large differences are seen in acute toxicity tests of IPDI monomer versus prepolymers. Bunge et al. (1977) reported LC50s for IPDI monomer of 160 mg/m3 in male rats and 135 mg/m3 in female rats.[14] In contrast, those authors report LC50s exceeding 5000 mg/m3 for IPDI polyisocyanate.

The Isocyanates Profile should be corrected to indicate that the evidence indicates prepolymers are significantly less toxic than the associated monomers.

[11] Mobay Inc. (1988). 90-Day inhalation toxicity study with 1,6-hexamethylene diisocyanate in rats with attached appendices and cover letter dated 01/18/1989. Study No. 81-141-01. TSCATS/401508. EPA/OTS Doc. No. 86-890000080.

[12] Pauluhn, J. and U. Mohr (2001). Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymers (HDI-IC and HDI-BT): Results of subacute and subchronic repeated inhalation exposure studies. Inhalation Toxicology 13:513-532.

[13] Mobay Inc. (1989). Chronic inhalation toxicity and oncogenicity study with 1,6-hexamethylene diisocyanate (HDI) in rats (final report) with attached appendices and cover letter dated 12/20/1989. TSCATS/405187. EPA/OTS Doc. No. 86-900000055.

[14] Bunge, W., H. Ehrlicher, and G. Kimmerle (1977). Medical aspects of work with surface coating systems using the spraying technique. Special Edition Zentralblatt fur Arbeitsmedizin Arbeitsschutz, Prophylaxe und Ergonomie, 2nd ed., Vol. 4, Dr. Curt Haefner Verlag GmbH, Heidelberg, Germany.