Received 9/15/04

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September 8, 2004

American Chemistry Council *Good Chemistry Makes It Possible*

Information Quality Guidelines Staff
Mail Code 2811R
U.S. EPA
1200 Pennsylvania Avenue, NW
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Dear Madam or Sir:

The American Chemistry Council Aliphatic Diisocyanates Panel (Panel) is writing to request correction of information posted by EPA on its Design for the Environment (DfE) website[1] concerning health effects of diisocyanates. The Panel includes major domestic manufacturers of aliphatic diisocyanates.[2]

The Isocyanates Profile,[3] included on the DfE website, is a part of the DfE Automotive Refinishing Partnership page.[4] The Isocyanates profile includes a section titled "Toxicology."[5] This section contains several incorrect statements.

1) Diisocyanate Health Endpoints. The opening of the Toxicology section states: "Diisocyanates are extremely reactive. Although they may affect many organ systems, the primary target of toxicity is the upper and lower respiratory tract." The Panel agrees that the primary target of toxicity is the upper and lower respiratory tract. It believes, however, that it is incorrect to state that diisocyanates affect many organ systems. In fact, the various studies on diisocyanates indicate that they have little or no systemic toxicity. For example, the primary study EPA has used to develop a reference concentration for hexamethylene diisocyanate (HDI)

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1 http://www.epa.gov/dfe

2 The Panel members are Bayer MaterialScience LLC and Rhodia Inc.

3 http://www.epa.gov/dfe/pubs/auto/profile/index.htm

4 The "Automotive Refinishing Partnership" page of the DfE website (http://www.epa.gov/dfe/projects/auto/index.htm) has a link labeled "Diisocyanates, the leading cause of occupational asthma." The link goes to the "DfE Publications" page, which in turn has a link to "Automotive Refinishing Partnership" documents. One of the listed documents is "Automotive Refinishing Industry: Isocyanates Profile, EPA Environmental Technology Initiative," and a link goes to Isocyanates Profile page.

5 http://www.epa.gov/dfe/pubs/auto/profile/chap2&a.pdf

is Mobay (1989), a two-year inhalation study in rats.[6] EPA states of this study: "Compound-related histopathological changes were limited to the respiratory tract, principally the nasal cavity."[7] Reproductive and developmental studies of HDI have found no significant effects.[8]

Therefore, the Isocyanate Profile should be corrected by removing the phrase "Although they may affect many organ systems" from the first paragraph of the Toxicology section.

2) Distinction between Aromatic and Aliphatic Diisocyanates. The first sentence of the Conclusions of the Toxicology section states: "There apepars [*sic*] to be little or no difference between aromatic and aliphatic diisocyanates for the above-listed endpoints." However, the information contained in the Toxicology section itself demonstrates differences with respect to carcinogenicity potential. As indicated on the website, there is some (although not conclusive) evidence of rodent carcinogenicity for three aromatic diisocyanates (toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI), and dianisidine diisocyanate (DADI)[9]). In contrast, no evidence of carcinogenicity was found in a two-year bioassay of the aliphatic diisocyanate, hexamethylene diisocyanate (HDI).

The first sentence of the Conclusions is contradicted by the later statement in the same paragraph that "it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates." This would include a generalization that there is "little or no difference between aromatic and aliphatic diisocyanates." The existing evidence suggests that there *is* a difference. Therefore, the Isocyanates Profile should be corrected to acknowledge the possible difference in carcinogenic potential between the aliphatic and aromatic diisocyanates.

3) Distinctions among Monomer, Prepolymer and Polymer. The Conclusions section of the Toxicology chapter states that "there are insufficient data available to make any major distinctions between polymeric and monomeric diisocyanates" and that "it appears that diisocyanate polymers exhibit the same respiratory tract effects as the monomers in repeated dose studies at similar doses." These conclusions flow from several incorrect statements in the Toxicology chapter concerning the composition and equivalence of diisocyanate monomers, prepolymers and polymers. For the reasons given below, there indeed

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6 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.

7 EPA (1994). 1,6-Hexamethylene diisocyanate (CASRN 822-06-0). Integrated Risk Information System, http://www.epa.gov/iris/subst/0638.htm.

8 Astroff A, Sheets L, Sturdivant D, Stuart B, Shiotsuka R, Simon G, and Andrews L (2000). A combined reproduction, neonatal development, and neurotoxicity study with 1,6-hexamethylene diisocyanate (HDI) in the rat. *Reproductive Toxicology* 14:135-146; Astroff A, Sturdivant D, Lake S, Shiotsuka R, Simon G, and Andrews L (2000). Developmental toxicity of 1,6-hexamethylene diisocyanate (HDI) in the Sprague-Dawley rat. *Teratology* 62:205-213.

9 The Panel is not aware of any commercial production or use for DADI.

are major distinctions between polymeric and monomeric diisocyanates, and the Isocyanate Profile should be corrected accordingly.

A) Nomenclature. As an initial matter, it appears the authors may have had some confusion between polymers and prepolymers. For clarity, the following terms will be used:

> A "polymer" is a substance where each molecule is made of many repeating structural units, and the various molecules are of varying molecular weights (that is, the number of repeating units varies). Fully-reacted diisocyanate-based polymers are primarily substances known as polyurethanes – two component polymers made by reacting diisocyanate monomers or prepolymers with polyols. There are also fully-reacted single-component diisocyanate-based polymers known as polyisocyanurates. There are no reactive isocyanate groups in a fully-reacted diisocyanate-based polymer – all isocyanate groups were reacted during the formation of the polymer.
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> A "monomer" is the starting unit from which the polymer is formed. An aliphatic diisocyanate monomer consists of an aliphatic hydrocarbon chain (straight-chained or cyclic) with two isocyanate groups.[10]
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> "Oligomer" is used to refer to a substance in which each molecule is made up of several repeating structural units. It can be thought of as a start on a polymer, but it does not have enough repeating units to qualify as a polymer. Unlike the fully-reacted diisocyanate-based polymer, the oligomer molecules may still have reactive isocyanate units.
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> The term "prepolymer" is usually used to refer to short chain oligomers made from at least two different monomers, e.g., HDI with glycols. For aliphatic diisocyanates, the term "prepolymer" is also sometimes used to refer to what is technically a homopolymer, or polyisocyanate.
>
> A "homopolymer" is a short chain oligomer made from a single monomer (versus a prepolymer made from two or more monomers). Diisocyanate homopolymers are known as "polyisocyanates."

B) Monomer Content in Prepolymers and Polymers. Under "Repeated Dose Respiratory Tract Toxicity", the Toxicology section states that there is a "high percent of monomer (>40%) in the polymer formations." In the conclusion, the website again states: "the polymers are known to have a high percentage of monomer in them." This is wholly inaccurate.

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[10] Unfortunately, the name of the monomer is sometimes used to refer to the prepolymer or polyisocyanate. Thus, for example, HDI technically refers to monomeric 1,6-hexamethylene diisocyanate. However, the term "HDI" will sometimes be used to refer to what is technically an HDI polyisocyanate. **CAS registry numbers or other means should be used to ascertain which species is the subject of any given study or report.**

HDI prepolymers (or polyisocyanates) contain only a small residual amount of monomer -- usually less than 1%. The trimer (isocyanurate trimer) form of HDI polyisocyanate contains less than 0.2 % of residual monomer, and this amount is stable over time. The biuret form contains approximately 0.5% when first manufactured; during storage this amount may rise to as much as 1.6% if temperatures are high (>120 F). Thus, in any circumstance, residual monomer in an HDI prepolymer (polyisocyanate) is less than 2%. HDI prepolymers are isocyanate-terminated, leaving functional isocyanate groups that can react with polyols or other substances.

IPDI-based polyisocyanates are typically isocyanurate trimer homopolymers of IPDI. They usually contain less than 0.5% monomeric IPDI at the time of manufacture, and, like the HDI isocyanurate polyisocyanates, their monomer content is stable over time.

A fully-cured polymer (polyurethane or polyisocyanurate) contains no residual monomer. It also has no functional isocyanate groups – all such groups are reacted in the formation of the polymer.

The Isocyanates Profile should be corrected to indicate the low amount of monomer in prepolymers and the lack of monomer in cured polymers.

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/m^3 in male rats and 135 mg/m^3 in female rats.[14] In contrast, those authors report LC50s exceeding 5000 mg/m^3 for IPDI polyisocyanate.

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

D) Differences in Toxicity of the Monomer and Polymer. A further incorrect statement in the Isocyanates Profile is: "In addition, also based upon a very limited data set, it appears that diisocyanate polymers induce the same effects in repeated dose studies as the monomer, at similar doses."

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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.

Regardless of whether there may be limited data on polymers, the existing data do not support the statement that they induce the same effects as the monomer. Woolrich (1982)[15] summarized data on finished polyurethane products as showing they are physiologically and chemically inert. Although there was a report of effects from polyurethane foam dust, subsequent studies have not validated that report. As explained above, diisocyanate polymers contain no reactive diisocyanate groups. Like other polymers, they are very large molecules that would be expected to be essentially inert.

It seems most likely that the Isocyanates Profile statement was based on studies of monomeric MDI and the so-called polymeric MDI (PMDI). Although commonly used, the term polymeric MDI is a misnomer; PMDI is *not* a polymer, but a prepolymer. Typically, PMDI consists of about one-half MDI monomer and one-half MDI oligomers. The similarity of effects for MDI and PMDI may be due to monomer content of the PMDI, but that does not apply to the final polymer made from either pure MDI or PMDI.

As discussed above, large differences are seen in studies of aliphatic diisocyanate monomers and prepolymers, and the polymers are essentially inert. Therefore, the statement that monomers and polymers produce similar effects should be deleted from the Isocyanates Profile.

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If used improperly, there can be real health risks associated with diisocyanates, and persons who work with such substances should be aware of those risks and means to mitigate them. However, such decisions should be based on complete and accurate information; otherwise, inappropriate decisions may be made. Misunderstanding of the relative toxicities of various forms of diisocyanates may also lead to inappropriate regulation. The Panel therefore believes it is important that the Isocyanates Profile be corrected as discussed above, and requests that EPA promptly do so.

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: Bill Hanson
Chief, Design for the
Environment Branch

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15 P. Woolrich (1982). Am. Ind. Hyg. Assoc. J. 43:A-20.