TOXICOLOGY

The Agency’s assessment of diisocyanate toxicity supports the need for exposure reductions. Diisocyanates are extremely reactive. Although they may affect other organ systems, the primary target of toxicity is the upper and lower respiratory tract. In addition, diisocyanates are known dermal sensitizers and, some are respiratory sensitizers. The following is a summary of the data derived from animal and epidemiological studies or case reports in humans.

For repeated dose studies, only information from inhalation studies has been included. Studies conducted by the oral route are not considered to be relevant because the oral route is not expected to be an occupational route of exposure nor are releases to water expected to result in exposures to diisocyanates because the diisocyanate moiety will hydrolyze in water.

Developmental and reproductive toxicity studies are not included in this profile because they are not the most sensitive endpoints for this class of compounds.

Repeated Dose Respiratory Tract Toxicity

Based on repeated dose studies in animals by the inhalation route, the monomeric diisocyanates, both aromatic and aliphatic, appear to be of high concern for pulmonary toxicity at low exposure levels. For monomers, effects on the respiratory tract (lungs and nasal cavities) were observed in animal studies at exposure concentrations of less than 0.005 mg/L. The experimental animal data available to the Agency on prepolymeric diisocyanates show similar adverse effects at levels that range from 0.002 mg/L to 0.026 mg/L.

There is also evidence that both aromatic and aliphatic diisocyanates are acutely toxic via the inhalation route.

Oncogenicity

Most members of the diisocyanate category have not been tested for carcinogenic potential. Commercially available Poly-MDI was tested in a 2-year inhalation study in rats. The tested material contained 47% aromatic 4,4’-methylenediphenyl diisocyanate (MDI) and 53% higher molecular weight oligomers. Interim sacrifices at one year showed that males and females in the highest dose group (6 mg/m³) had treatment related histological changes in the nasal cavity, lungs and mediastinal lymph nodes. The incidence and severity of degeneration and basal cell hyperplasia of the olfactory epithelium and Bowman’s gland hyperplasia were increased in males at the mid and high doses and in females at the high dose following the two year exposure period. Pulmonary adenomas were found in 6 males and 2 females, and pulmonary adenocarcinoma in one male in the high dose group. However, aliphatic hexamethylene diisocyanate (HDI) was found not to be carcinogenic in a two year repeated dose study in rats by the inhalation route. HDI has not been tested in mice by the inhalation route.
Though the oral route is not an expected route of exposure to humans, it should be noted that in two year repeated dose studies by the oral route, aromatic toluene diisocyanate (TDI) and 3,3'-dimethoxy-benzidine-4,4'-diisocyanate (dianisidine diisocyanate, DADI) were found to be carcinogenic in rodents. TDI induced a statistically significant increase in the incidence of liver tumors in rats and mice as well as dose-related hemangiosarcomas of the circulatory system and has been classified by the Agency as a B2 carcinogen. DADI was found to be carcinogenic in rats, but not in mice, with a statistically increase in the incidence of pancreatic tumors observed.

Respiratory and Dermal Sensitization

Based on the available toxicity data in animals and epidemiologic studies of humans, aromatic diisocyanates such as TDI and MDI are strong respiratory sensitizers. Aliphatic diisocyanates are generally not active in animal models for respiratory sensitization. However, HDI and possibly isophorone diisocyanate (IPDI), are reported to be associated with respiratory sensitization in humans. Symptoms resulting from occupational exposure to HDI include shortness of breath, increased bronchoconstriction reaction to histamine challenges, asthmatic reactions, wheezing and coughing. Hazardous Substance Database (HSDB, 1995) cites two case reports of human exposure to IPDI by inhalation that suggest IPDI is a respiratory sensitizer in humans. In view of the information from case reports in humans, it would be prudent at this time to assume that both aromatic and aliphatic diisocyanates are respiratory sensitizers. Studies in both human and mice using TDI, HDI, MDI and dicyclohexylmethane-4,4'-diisocyanate (HMDI) suggest cross-reactivity with the other diisocyanates, irrespective of whether the challenge compound was an aliphatic or aromatic diisocyanate.

At present, there appears to be no reliable animal model for testing for respiratory sensitization that gives an adequate correlation with human respiratory sensitization. In the absence of such a model, and in light of the conflicting animal and human data, it is prudent to assume that all diisocyanates have the potential to be human respiratory sensitizers.

Diisocyanates are moderate to strong dermal sensitizers in animal studies. There seems to be little or no difference in the level of reactivity between aromatic and aliphatic diisocyanates.

Dermal Irritation

Skin irritation studies performed on rabbits and guinea pigs indicate no difference in the effects of aromatic versus aliphatic diisocyanates. The level of irritation ranged from slightly to severely irritating to the skin. One chemical, hydrogenated MDI (1,1'-methylenebis-4-isocyanatocyclohexane), was found to be corrosive to the skin in guinea pigs.

Conclusions

In general, there appears to be little or no difference between aromatic and aliphatic diisocyanates for the above listed end-points. In addition, there are insufficient data available to make any major distinctions between polymeric (≤1000 MW) and monomeric diisocyanates. Based on repeated dose studies in animals by the inhalation route, both aromatic and aliphatic
diisocyanates appear to be of high concern for pulmonary toxicity at low exposure levels. Based upon a very limited data set, it appears that diisocyanate prepolymers exhibit the same respiratory tract effects as the monomers in repeated dose studies. There is also evidence that both aromatic and aliphatic diisocyanates are acutely toxic via the inhalation route. Most members of the diisocyanate category have not been tested for carcinogenic potential. Though the aromatic diisocyanates tested positive and the one aliphatic diisocyanate tested negative in one species, it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates. In the absence of more human data, it would be prudent at this time to assume that both aromatic and aliphatic diisocyanates are respiratory sensitizers. Diisocyanates are moderate to strong dermal sensitizers in animal studies. Skin irritation studies performed on rabbits and guinea pigs indicate no difference in the effects of aromatic versus aliphatic diisocyanates.

See the New Chemicals Program’s Category description for Isocyanate Compounds in Appendix A. Definitions of the terms “monomer,” “prepolymer,” and “polymer,” and “polyisocyanates,” are provided in Appendix A-1. A clarification of monomer content in prepolymers and polymers is provided in Appendix A-2.

May 1990; revised June 2005.
APPENDIX A

ISOCYANATE CHEMICAL CATEGORY

**Definition.** Any molecular structure containing two or more isocyanate groups is considered to be a member of the category for new chemical purposes:

\[ R-(N=C=O)_{2} \]

Members of the class include new isocyanate monomers as well as new oligomers, polymers, prepolymers, or reaction products of existing isocyanate monomers. Most new chemical isocyanates of concern are polymers or oligomers containing well-known diisocyanate monomers such as toluene diisocyanate (TDI) or methylenebis (p-phenylisocyanate) (MDI).

**Hazard Concerns.** Isocyanates are of concern for potential dermal and pulmonary sensitization, and other lung effects. Aromatic isocyanates may be potential carcinogens based on analogy to TDI or 3,3'-dimethoxybenzidine-4,4'-diisocyanate (dianisidine diisocyanate, DADI).

**Boundaries.** Structures with an isocyanate equivalent weight ≥ 5,000 are presumed not to pose a hazard under any conditions. Typically, concerns are confined to those species with molecular weights < 1,000. Based on submitted test data, the Agency does not have pulmonary sensitization concerns for polymers derived from m-tetramethylxylene diisocyanate (CAS# 2778-42-9) or a,a-dimethyl-m-isopropenyl benzyl isocyanate (CAS # 2094-99-7).

The new chemical program has thus far been concerned only with those isocyanates having potentially significant inhalation exposure.

Frequently, new chemical isocyanates are manufactured with a significant excess of isocyanate monomer. Under these circumstances, the excess monomer is usually regarded as more hazardous than the “new” chemical component, and these PMN substances are ordinarily not regulated under section 5 TSCA. A PMN substance is considered “existing” if more than 50% of the free isocyanate groups in the PMN substance (new chemical component + existing chemical monomer) reside on unreacted monomer(s).

**General Testing Strategy**

The following three tests are usually prescribed for isocyanates found to pose a potentially unreasonable risk:

- Dermal sensitization (40 CFR 798.4100)
- 90-day subchronic inhalation toxicity (40 CFR 798.2450)
- Pulmonary sensitization by either the Karol method (Toxicol. Appl. Pharmacol. 68:229-241, 1983) or the Sarlo and Clark method, level 3 & 4 (Fundamental & Applied
Toxicology 18:107-114, 1982) or an equivalent method.

May 1990; revised 1993; revised February 1995.
APPENDIX A-1

DEFINITIONS OF TERMS

(Editor’s Note: EPA has added Appendix A-1 to reference definitions of terms provided by the American Chemistry Council on September 8, 2004. <http://www.epa.gov/quality/informationguidelines/iqg-list.html>

This Appendix also contains definitions of monomers, prepolymer, and polyisocyanates as reported in the recent summary of diisocyanates health hazard evaluations published by the National Institute for Occupational Safety and Health (NIOSH) and the definition of “polymer” in the TSCA polymer exemption rule, 40 CFR 723.250(b)).

Definitions of Monomer, Prepolymer, Polymer, and Polyisocyanates and related terms:

1.) Nomenclature provided by the American Chemical Council’s Diisocyanates Panel.

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 prepolymer 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.

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.

“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.

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.”

2.) Definitions provided by National Institute for Occupational Safety and Health (NIOSH).

Diisocyanates (Monomers): The difunctional isocyanate species from which polyisocyanates and polyurethanes are derived. Common examples of monomeric isocyanates include 1,6-hexamethylene diisocyanate (HDI), 2,4- and/or 2,6-toluene diisocyanate (TDI), 4,4’ diphenylmethane diisocyanate (MDI), methylene bis (4-cyclohexylisocyanate) (HMDI), isophorone diisocyanate (IPDI), and 1,5-naphthalene diisocyanate (NDI). Commercial-grade TDI is an 80:20 or 65:35 mixture of the 2,4- and 2,6-isomers of TDI, respectively.

Polyisocyanates: Species possessing free isocyanate groups and derived from monomeric isocyanates either by directly linking these monomeric units (a homopolymer) or by reacting these monomers with di- or poly-functional alcohols or amines (a copolymer).

Prepolymers: Species possessing free isocyanate groups, prepared from the reaction of a polyol with an excess of di- or polyisocyanate. Commercially available isocyanate products frequently contain prepolymers in lieu of more volatile isocyanate monomers.

Oligomeric Isocyanates (Oligomers): Relatively low molecular weight polyisocyanates.

Intermediates: Species possessing free isocyanate groups, formed during use of an isocyanate product by partial reaction of the isocyanate species with a polyol.

3). Polymer definition: TSCA Polymer Exemption Rule, 40 CFR 723.250(b)

Polymer - a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units and comprising a simple weight majority of molecules containing at least 3 monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units.
APPENDIX A-2

CLARIFICATION OF MONOMER CONTENT IN PREPOLYMERS AND POLYMERS

(Editor's Note: EPA has added Appendix A-2 to include information on the monomer content in prepolymer and polymers provided by the American Chemistry Council on September 8, 2004. <http://www.epa.gov/quality/informationguidelines/iqg-list.html>.)

HDI prepolymer (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 prepolymer is 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.