American Chemistry Council | Diisocyanates Panel

A REVIEW OF WHETHER DERMAL EXPOSURE TO DIISOCYANATES CAUSES OCCUPATIONAL ASTHMA

INTRODUCTION

Diisocyanates are considered to be dermal sensitizers and, in some individuals, may cause allergic contact dermatitis rash. It appears to be an infrequent event, however, as there are only a few reports of diisocyanate contact dermatitis.[1] The ability of diisocyanates to induce respiratory sensitization in some individuals is also a known potential adverse health effect in humans, but evidence indicates sensitization occurs after inhalation exposure to concentrations above workplace exposure limits.[2] The clinical symptoms of respiratory sensitization that may occur after a subsequent inhalation exposure in some individuals are wheezing, shortness of breath, and chest tightness. Exposure to diisocyanates is most likely to occur in the work environment. Respiratory sensitization that is caused or worsened by breathing in substances on the job is typically termed "occupational asthma."[2] The role that dermal contact with diisocyanates plays in the development of diisocyanate-related occupational asthma, however, remains unresolved for humans.

ISSUE SUMMARY

Sensitization is a two-fold process: 1) induction or sensitization of the individual's immune system to an agent or allergen; this may take multiple exposures over some period of time; 2) a subsequent exposure or "challenge" (also called elicitation) which produces the clinical symptoms. The symptoms of dermal sensitization are a skin rash and dermatitis, whereas the respiratory sensitization symptoms are wheezing and shortness of breath.

Although there has been research in the area for over 40 years, there is still no validated experimental animal model accepted by regulatory agencies that adequately reflects the respiratory sensitization process and numerous symptoms associated with occupational asthma. Several research studies have demonstrated respiratory changes (e.g., alterations in respiratory rate, non-specific respiratory reaction to methacholine, influx of inflammatory cells) and/or antibody production in animals after dermal induction exposure and subsequent inhalation challenge with MDI or TDI.[3,4,5,6,7,8,9]

One respiratory sensitization study model using Brown Norway rats involving dermal applications with MDI for induction demonstrated the existence of a threshold for the elicitation of respiratory hypersensitivity responses following inhalation challenges.[9] A high-dose MDI dermal induction protocol demonstrated a neutrophilic and eosinophilic inflammatory response in the lung following repeated inhalation challenge to MDI. These dermally "sensitized" rats did not exhibit pulmonary effects in the absence of inhalation exposure, and marked respiratory changes were only observed after repeated inhalation challenges using irritating concentrations of MDI aerosol.[10] It was also demonstrated in the same study, that at least three to four

adequately spaced challenge exposures using moderately irritant concentrations of MDI are required, after multiple dermal induction applications, to elicit a typical asthma response. In another study animals, sensitized by the intradermal route only, responded during challenge when an irritating concentration of MDI (>20mg/m^3) was used.[4] Experimental evidence in animals suggests that the mechanism of diisocyanate-induced asthma may require at least two potentially independent processes: 1) a sequence of immunological pathways which activate or "sensitize" the individual's immune system to an agent or allergen which may occur following dermal or inhalation exposure, and 2) airway irritation by inhalation exposure.[10]

In a study by Mapp and others, guinea pigs were sensitized by three weekly intradermal injections of TDI or saline and then challenged by inhalation of TDI seven days after the last injection. The results of this study suggests that intradermal induction can sensitize guinea pigs and cause an inflammatory response as well as IgG production after inhalation challenge, but also that irritation plays a role in the mechanism of TDI asthma.[8]

Animal study data and evidence from diisocyanate workplaces on this issue have been considered by experts.[11] They concluded that evidence demonstrated that dermal exposures to MDI and TDI can cause induction of sensitization by activating the immune system in animals and humans. However, experimental animal studies suggest that dermal exposure without a subsequent inhalation exposure of the respiratory tract is not sufficient to initiate a respiratory sensitization (or asthmatic) response.

CONCLUSION

In conclusion, dermal sensitization through activation and responses of the immune system can be triggered by MDI and TDI and whether such dermal exposure can lead to a respiratory disease state (e.g., diisocyanate-specific occupational asthma) remains to be clarified. Regardless of the route of induction of "sensitization," inhalation exposures are necessary to initiate the subsequent respiratory response. Thus, the role that dermal contact with diisocyanates plays in the development of occupational asthma remains unresolved for humans. As a result, it continues to be prudent to minimize dermal exposure to isocyanates.

REFERENCES

[1] Goossens, A., Detienne, T., and Bruze, M. (2002). Occupational allergic contact dermatitis caused by isocyanates. *Contact Dermatitis*, 47, (5), Nov., 304-8

[2] Ott, M.G., Diller, W.F., Jolly, A.T. Respiratory Effects of Toluene Diisocyanate in the Workplace: A Discussion of Exposure-Response Relationships. Crit Rev Toxicol. 2003; 33 (1): 1-59.

[3] Pauluhn, J. (1994). Test methods for respiratory sensitization. *Arch Toxicol Suppl*., *16*,77-86.

[4] Pauluhn, J., & Mohr, U. (1994). Assessment of respiratory hypersensitivity in guinea-pigs sensitized to diphenylmethane-4,4'-diisocyanate (MDI) and challenged with MDI, acetylcholine or MDI-albumin conjugate. *Toxicology, 92* (1-3), 53-74.

[5] Rattray, N.J., Botham, P.A., Hext, P.M., Woodcock, D.R., Fielding, I., Dearman, R.J., Kimber, I. (1994). Induction of respiratory hypersensitivity to diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. *Toxicology, 88*, 15-30.

[6] Pauluhn, J. (1995). Diphenylmethane-4,4'-diisocyanate (MDI-monomer). Evaluation of respiratory sensitization in guinea pigs following brief, high-level inhalation induction exposure and challenge with ramped MDI-concentrations. International Isocyanate Institute, Manchester. *III Report No. 11184.*

[7] Blaikie, L., Morrow, T., Wilson, A.P., Hext, P., Hartop, P.J., Rattray, N.J., Woodcock, D., Botham, P.A. (1995). A two-centre study for the evaluation and validation of an animal model for the assessment of the potential of small molecular weight chemicals to cause respiratory allergy. *Toxicology, 96*, 37-50.

[8] Mapp, C. E., Lucchini, R. E., Miotto, D., Chitano, P., Jovine, L., Saetta, M., Maestrelli, P., Springall, D. R., Polak, J., and Fabbri, L. M. (1998). Immunization and challenge with toluene diisocyanate decrease tachykinin and calcitonin gene-related peptide immunoreactivity in guinea pig central airways. *Am.J.Respir.Crit.Care.Med*., 158, 263-9.

[9] Pauluhn, J., & Poole, A. (2011). Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): Determination of the elicitation threshold concentration of after inhalation sensitization. *Toxicology, 281*, 15-24.

[10] Pauluhn, J. (2005). Brown Norway Rat Asthma Model of Diphenylmethane 4,4'-Diisocyanate. *Inhalation Toxicology*, *17*,729–739.

[11] Graham, C., Ott, M. G., Hoffmann, H-D., Shiotsuka, R. N., Davies, P., Landry, T. D., & Collins, M. A. (2002). Respiratory sensitization: the role of dermal contact with MDI and TDI. *GIL Report 2002/D*. Gilbert International Ltd., Manchester, UK.