

VII. RESEARCH NEEDS

Information needed to develop a standard for occupational exposure to the diisocyanates is incomplete in many respects. It has been necessary to recommend a standard for the diisocyanates based on similarities to TDI and MDI, since adequate information is not available on other diisocyanates to demonstrate that they differ appreciably in their toxicity.

Detailed epidemiologic studies are needed to determine the long-term health effects of occupational exposure to diisocyanates and safe levels for such exposures. These studies should relate respiratory symptoms, pulmonary function data, and other health effects to actual individual exposures and should include long-term followup of persons leaving the workforce for health reasons.

Studies are required to ascertain whether all of the diisocyanates are sensitizing agents and whether they can produce cross-sensitization. Karol et al [62,110] have developed a test antigen by conjugating p-tolyl isocyanate with a protein carrier that has made it possible to demonstrate the existence of hapten-specific antibodies in workers exposed to TDI. Similar antigens would be useful for investigating the sensitizing properties of other diisocyanates, both in exposed workers and in animal studies.

Particularly needed are dose-response studies of sensitization to the diisocyanates to determine whether sensitization can result from long-term exposures at low concentrations and to investigate the relationship of length of exposure to the development of sensitization. These relationships could be studied in guinea pigs exposed to TDI, using the p-tolyl isocyanate antigen [110] to test for the induction of tolyl-specific antibodies. Sera from these animals should not be pooled, so that the standard deviation can be determined. Changes in respiratory response in exposed animals should also be evaluated to determine their correlation with the appearance of IgE or IgG antibodies. As a corollary experiment, animals should be exposed at the same total dose administered over varying time periods to simulate the effects of excursions while retaining the same 8-hour TWA exposure; eg, groups of animals might be exposed at 5 ppb for 8 hours, 160 ppb for 15 minutes, and 2,400 ppb for 1 minute.

To improve protection of exposed workers, it is particularly desirable to determine whether there are intrinsic, predictable differences between sensitizable and nonsensitizable individuals. The studies of Butcher et al [63,65], showing that persons sensitized to TDI tend to be hyperreactive to bronchoconstrictors such as mecholyl, appear to offer promise in this regard. It is necessary to determine whether this hyperreactivity is a result of exposure or a preexisting factor that may indicate a predisposition to become sensitized to diisocyanates. Methods of identifying sensitized individuals before overt chronic symptoms develop should also be explored. The value of measurements of eosinophilia and cyclic AMP and of

pulmonary function studies and immunologic testing as diagnostic tools should be carefully evaluated, since existing reports of their usefulness are contradictory. The p-tolyl isocyanate test antigen developed by Karol and her colleagues [62] appears to be a particularly useful diagnostic tool for TDI sensitization, and analogous antigens should be developed for investigating sensitization to other diisocyanates.

Because the diisocyanates may be highly reactive biologically, it is important that their potential to cause carcinogenic and mutagenic effects be investigated. Mutagenicity screening in microbial tests should be carried out, using a test protocol that will decrease the likelihood of hydrolysis to possibly mutagenic amine intermediates. Diisocyanates, especially those that are positive in mutagenicity tests, should also be tested for carcinogenicity in animal experiments. Studies of absorption, distribution, metabolism, and excretion of diisocyanates are also needed to elucidate the mechanism of their action.

The consequences of exposure to the aerosols produced in many diisocyanate applications, such as spraying, should also be investigated. It has been assumed that reactive diisocyanates in aerosol form produce the same biologic consequences as diisocyanate vapors at equivalent concentrations. This assumption should be experimentally verified. Similarly, most applications of diisocyanates involve simultaneous exposure to other toxic chemicals, and inadequate information is available on the role of these chemicals in producing observed health effects in diisocyanate workers and their possible additive or synergistic nature.

Reliable, sensitive continuous monitoring methods should be developed for all the diisocyanates. The paper-tape method developed by Reilly [136] is a valuable method for continuous monitoring of the aromatic diisocyanates, particularly TDI. Comparable methods are needed for other diisocyanates to protect workers from dangerous excursions and to provide better information relating health effects to actual exposures.

VIII. REFERENCES

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