SMALL PLANTS AND THEIR MEDICAL PROBLEMS— THE FURNITURE INDUSTRY

Respiratory Health Effects of Isocyanates

Hans Weill, MD

Occupational asthma has become well-recognized in association with organic dust exposure. There is now an interest in the capability of simple chemicals to induce bronchospasm in a susceptible portion of the work population.

A little more than five years ago it was our good fortune to study an industrial population both before exposure and in a follow-up five years after exposure. We were called in prior to the opening of a new plant that was to manufacture toluene diisocyanate. There was a genuine effort by the medical department of the plant to exclude individuals having a history of asthma or allergy; but, as you will see, that is very difficult—probably impossible—to do clinically. Nonetheless, we suspected that there were some people who would become intolerant; we wanted to find out from those people what causes this intolerance and what might we do to deal with the mechanism. We also hoped to address the question concerning a general effect of TDI on respiratory health; in other words, is there an irritant effect on the airways that can be associated with early development of bronchitis or other airways' problems quite apart from susceptibility or sensitization? We borrowed from the United Kingdom their new methodology for measuring airborne concentrations of TDI vapor. It's a physico-chemical method wherein a chemically impregnated tape-cassette unit permits 8-hour continuous monitoring of TDI vapor.

As one might anticipate, about 5% of the exposed population did indeed become intolerant of TDI. This percentage is consistent with the other limited data in the literature. Some of these people were smokers. Some had an atopic history, some had positive skin tests to the ordinary environmental irritants, some had a known major exposure that had been recognized a week or so earlier, some developed symptoms very shortly after an exposure and some took months. Very few additional people out of a total of 12 have become susceptible in this cohort over the 5-year period. Most of the people develop their symptoms in the first year of exposure. In many cases the clinical picture of susceptibility to sensitization was not entirely convincing or clear; thus, we performed inhalation provocative challenge testing, first using very low doses 0.005 ppm and then going to doses of 0.01 and 0.02 ppm. Contrary to some investigators, we never exposed anyone to concentrations either above the threshold limit value of 0.02 ppm or above those levels that were actually found in the plant. In the population that was believed to be active, we got positive results and usually one of several patterns emerged. Either they had an immediate drop in ventilatory capacity—ie, expiratory airway flow—with prompt reversibility, there was a late response (within 4, 6 or 8 hours) or there might be a gradual decline in ventilatory capacity. All occupational asthmas that I'm aware of characteristically have a dual response—ie, an immediate drop in flow and then a late drop; usually the late drop is slow to emerge. In three individuals there seemed to be a dose-response relationship. As in other types of

occupational asthma, these persons' reactions were blocked by the pre-treatment with cromolyn sodium. That doesn't mean that reactive individuals should be kept in a TDI environment, having to take this medication everyday, but at least there is an available remedy for the occasional problem and it's a good thing to know.

Usually substances like TDI don't cause IgE-mediated, immediate type, reagin-mediated asthma unless the substance binds with protein. We did bind TDI with human serum albumin and employed it on our population. The RAST test, used to measure specific IgE, indicated that IgE antibodies were not present in significant quantity. Cells were not stimulated normally by isoproterenol to release cyclic AMP—which has a bronchodilator effect—in the presence of TDI. TDI at certain concentrations acts as a partial agonist on lymphocytes to stimulate the release of cyclic AMP; at lower concentrations it can block the release. This was the first evidence that something may be awry in the adrenergic function of cells when TDI is present. Persons who had a good clinical picture and were positive on challenge with TDI differed from controls in their responsiveness to methacholine, a nonspecific bronchoconstrictor. Something seems to happen to the cells of TDI-reactors in that there is a flattened dose-response relationship to release of cyclic AMP by the materials that are known to stimulate this release.

Recently, Dr. Yves Alarie at the University of Pittsburgh has developed what he believes is a suitable in vitro test procedure for TDI sensitivity using a normal isocyanate (TMI) together with the RAST test. He claims a rather high specificity for the test, but Dr. Brian Butcher (of Tulane) has found that only about 15% of his reactors had a positive RAST using Alarie's allergen. Inasmuch as we were not able to confirm Alarie's work, we are rather uncertain about the possibility of this test.

A 5-year longitudinal study dealing with the epidemiology, dose vs biologic response (measured serially with lung function), questionnaires, etc, has been completed and the final report will be available shortly from NIOSH. Longitudinal studies such as this are going to be conducted more frequently as various populations are studied over the course of time.

We have had an enviable opportunity in working with a "virgin" population, one that could be assessesd prior to TDI exposure as well as over a period of time subsequent to exposure. There are some problems in any longitudinal study; the analytical part of our study was difficult, but we are convinced that the data are good and valid, and they provide some insight into the longitudinal course of workers exposed in this chemical setting. TDI was certainly not the only chemical produced or airborne in the work environment, yet we feel reasonably sure that the disease symptoms were TDI-related.

Throughout the 5-year period of the study, TDI concentrations fluctuated; at times they were higher than the current TLV for short periods. During a plant or process overhaul, exposures were particularly likely to be elevated. It's important to recognize that TDI-intolerant people shouldn't be in such areas during these episodes. The exposures seemed to have no systematic trend but had a random variation.

The annual declines in FEV_1, FEV% (ie, the ratio) and the FEV midflow ($FEV_{25/75}$) are significantly related to TDI dose after controlling for smoking and atopic status. Dose is measured either by cumulative exposure or according to the exposure time spent above a certain peak level. In both instances, those in the higher exposure groups had a significantly greater decline. The FEV_1 annual decline and FEV% for the higher exposure category was not significantly different from predicted annual declines for

members of the general population. They are, however, significantly greater than the annual declines in the lower exposure groups. Both the $FEV_{25/75}$ and the FEV_{50} were significantly greater than expected in both exposure categories. This is not an exposure-related effect but was found in the total chemical manufacturing cohort; these values were higher annual changes if compared to cross-sectional predicted data. The diffusion constant was greater than expected, but there was a negative correlation that was very hard to explain. TDI dose, measured either cumulatively or at peak exposures, gave the same thing in terms of correlation with lung function change. FEV_1, FEC, RV and RV_2 showed changes that were significantly related to smoking. The prevalence of both bronchitis and dyspnea increased greater in the high exposure (cumulative) group than in the low groups; these differences, however, were not statistically significant.

Neither atopy nor smoking served to identify persons who might be at high risk of developing TDI sensitivity. Some TDI reactors failed to attain pre-exposure or pre-sensitization values (ie, FEV_1, $FEV_{25/75}$) despite their transfer to other areas in the chemical complex. Every effort was made to put them as far away from TDI as possible, but it is difficult to remain upwind of all emissions in a complex chemical plant. There is also persuasive evidence that some people have the clinical picture of sensitization but without a positive reaction to inhalation provocative testing.

OCCUPATIONAL SAFETY AND HEALTH SYMPOSIA

1979

Department of Environmental, Public
and Occupational Health

American Medical Association
Chicago, Illinois 60610

Contract #210-79-0009

US DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Division of Technical Services
Cincinnati, Ohio 45226

June 1980

DISCLAIMER

The contents of this report are reproduced as received from the contractor. The opinions, findings, and conclusions expressed are not necessarily those of the National Institute for Occupational Safety and Health, nor does mention of company names or products constitute endorsement by the National Institute for Occupational Safety and Health.

These proceedings are based upon the manuscripts submitted in accordance with NIOSH Contract No. 210-79-0009 with the American Medical Association.

NIOSH Project Officer: Loren L. Hatch, DO, PhD
Principal Investigators: Jermyn F. McCahan, MD
Robert H. Wheater, MS

DHHS (NIOSH) Publication No. 80-139