HUMAN PULMONARY FUNCTION STUDY (5 YEARS) ON OCCUPATIONAL ISOCYANATE EXPOSURE

by

Hans Weill, M.D.
Department of Medicine
Tulane University School of Medicine
New Orleans, Louisiana

ABSTRACT

A previously unexposed industrial cohort in TDI (toluene diisocyanate) manufacturing was investigated over a 5-year period with collection of environmental and biologic response data. In addition to scientific questions addressing the incidence, determinants and mechanism of susceptibility to low levels of TDI vapor (between 4 and 5 percent of the population became TDI "reactors"), attention was directed toward the possibility that a general adverse effect on airways function might occur in this population of 223 men. Extensive personal monitoring characterizing the exposures of 42 jobs through 2000 continuous 8-hour personal samples allowed the individual reconstruction of cumulative exposure in each study participant. Measurement of lung function included lung volumes, maximum expiratory flow rates and diffusing capacity. Lung function testing was performed at the plant site on nine different occasions over the 5-year period, using the mobile pulmonary function laboratory.

Smoking adversely influenced the longitudinal decline of ventilatory function (FVC and FEV_1). After accounting for smoking and atopic status, significant differences between exposure categories were found for annual declines in FEV_1 FEV percent, and FEF_{25-75}. The exposure-related effect on annual declines in these measurements of expiratory flow was slight in the total population, but when the study group was divided by smoking history it was found that the exposure-related effect was confined to the nonsmokers and masked or not present in the smokers. Additionally, some TDI reactors have failed to attain preexposure or presensitization values of FEV_1 or FEF_{25-75} despite transfers to other areas in the chemical complex.

I am going to present a brief summary of a study that was recently reported to NIOSH in final form. This report will be available to the public.

In 1973 with the support of the National Institute of Occupational Safety and Health, and with the cooperation of a major chemical company, the members of my unit were invited to engage in a five year prospective

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longitudinal study of a working population exposed to TDI, toluene diisocyanate. This population works in a process which occurs before the foaming process that was discussed in the previous presentation. TDI manufacturing had not previously been a part of the manufacturing operations of this chemical plant in southwest Louisiana. We had a unique opportunity to study a population before their exposure.

The purpose of this very complex study, a multi-disciplinary study, was to determine the influencing factors in any acute or chronic respiratory effects that may emerge from this exposure.

There were initially 168 members of this working population in the TDI plant. In the first two years of this study, new members of the work force engaged in this aspect of the manufacturing were added to the cohort. Ultimately, 277 people were available for study. These individuals were studied at various times over a 5-year period, not at each of the observation points, but with a minimum number being required for inclusion in the data analysis.

The TDI plant that we studied cost about $60 million to build in the early to mid-1970's. At that time gaskets were not too expensive, but TDI spills caused by bad gasketing occurred. When a large leak occurs there is, of course, a very high vapor concentration of this volatile material.

One of the known effects of exposure to isocyanates, either in manufacturing or in foaming operations, is an acute respiratory disease, properly called "asthma." TDI produces intolerance, at times, to low levels of exposure. In our population between 4 and 5 percent of the population became intolerant. Age and smoking status varied among the individual workers, but smoking did not seem to be an important influencing factor in producing intolerance. Some workers had positive TDI bronchial provocation challenges in the lab, whereas some did not, at the levels of exposure that we used. Some were atopic, that is they had an allergic diathesis, as was indicated by two or more positive skin tests to common inhalant allergens whereas others were not. Those eliciting a positive response were about what you would expect in the general population; therefore, atropy was not an important influencing or predicting factor.

Some individuals had known exposures to high concentrations of TDI; some individuals developed symptoms as early as less than a week after the first exposure, whereas others took as long as a couple of years to first develop these symptoms. Most of these individuals did have complaints in the first year.

We were able to reproduce the bronchial spasm in the laboratory with varying patterns, as have other researchers. By carefully monitoring the levels of exposure and following the medical course using workers' respiratory status and various patterns of bronchial provocation, a pattern emerged. An acute response, where a drop in ventilatory capacity occurs immediately after a 15-minute exposure, or a late response, where a drop may occur some hours later and is usually less readily reversed, or a dual response of both an acute and a late response may develop.

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TDI is a simple chemical and if it acts as an allergen, it presumably acts as a haptene that must be conjugated with a protein. By using what was touted to be, perhaps, an advanced rash test (developed at the University of Pittsburgh) that measured specific Ig antibodies, we found that only 15 or 18 percent of our acute reactors did in fact, have positive tests. We could not demonstrate that IgE allergy, the classical asthma type allergy, was the important factor in the mechanism of most of these instances.

Something did seem to happen in these people at the cellular level. The ordinary release of cyclic AMP by mast cells, which is good for the bronchi, dilates the bronchi. When stimulated with known activators of cyclic AMP, the response is limited. There seems to be an alteration of the dose response curve for the cyclic nucleotide. For some reason, people who have become reactive have a depressed release or ability to release cyclic AMP. We do not know exactly why 4 to 5 percent of an exposed population become intolerant.

What about the outcome of these acute problems? A followup of these acute reactors, shows two measurements of expiratory flow, even after sensitization was recognized. After the workers were ostensibly removed from exposure, approximately 40 percent of these reactives continued to have unanticipated declines in their ventilatory function. This suggested to us that some long-term effects may occur even after exposure ceases.

This has also recently been found with western red cedar dust exposure and other causes of occupational asthma. Investigators in Vancouver found that removing these individuals from exposure did not always lead to complete reversal of their disease.

We were interested in characterizing exposure to TDI, to learn its more general effect on respiratory health and the development of dose response relationships. Initially, we measured exposure with a continuous monitor using a chemically impregnated paper tape. In the first 2 years, there were frequent excursions above 0.02 parts per million in both production areas and in drumming.

In the last three years, we were able to develop personal sampling information. We would produce 8-hour continuous profiles of the workers' isocyanate vapor exposure. There was considerable variability and fluctuation in the exposure over an 8-hour shift. We performed 1,949 characterizations of the personal exposures of persons representing 42 job titles, to reconstruct for each individual a personal cumulative exposure to use to correlate with the biological events that we saw. If you take 1,949, 8-hour time-weighted samples, and perform a frequency distribution in various concentrations (parts per billion), you see a marked skewing. The distribution becomes more symmetrical if you convert this to a large scale. We were then able to develop high, moderate, and low exposure categories. Ultimately, we were able to generate exposure categories for each of these 42 jobs. Then, by finding out who worked where and when, each individual was, by summation, assigned an exposure profile. In a healthy population the percent predicted for measurement of expiratory flow, lung volumes, and diffusing capacity is nearly 100 percent. The average annual change of forced

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expiratory volume in one second, a very stable measurement, will be used to illustrate changes in the population studies. As an indicator of long-term air-ways effect we used the annual change in lung function, by exposure groups. Using this method we found the smoking effect which would be expected and an exposure effect. We found a significant effect on average annual change in lung function by TDI exposure in people who never smoke; a difference in average annual change of somewhat less than 40 milliliters per year. The high exposure group had about the same decline per year as the smokers. In the ex-smokers and the current smokers the trend was in the same direction, but there was some masking of this exposure-related effect, which was significant in the people who never smoked.

This is not the first time an occupational exposure effect has been demonstrated only in non-smokers. It is commonly held that smoking enhances an exposure effect. But it does not necessarily have to do that, especially when we are dealing with air-ways disease and not malignancy. The effect here, fairly stated, is a small effect. The average annual decline in FEV_1 and other expiratory flows, showed about the same results based on cross-sectional predicted data. It is only about 27 or 30 milliliters per year, and the high exposure group did not exceed that level very much. In longitudinal studies, however, that decline may be smaller but even so, it is a small effect. It is a modest effect and we think it is related to exposure, after such things as smoking and atrophy are accounted for in the regression equations.

In conclusion we have demonstrated that there are substantial exposures in this manufacturing operation. Both continuous area and personal monitors have demonstrated that essentially everybody in this study had at one time or another been exposed. Over the 5-year period, there was no systematic exposure trend demonstrated. We found that these various expiratory flow rates, which are measurements or indicators of air flow function or obstruction, are significantly related after controlling for smoking and atopic status to TDI dose. The same significance was established whether or not we measured dose by cumulative method or time spent above a certain level. As I have already mentioned, these expiratory flows were not significantly different from the annual declines from cross-sectional studies. But these particular expiratory flows were significantly greater than those prediction values would lead you to expect. There was a smoking effect, which helped to validate these longitudinal data. And, as I have already mentioned, the effect of TDI exposure of FEV_1 annual change or other expiratory flows appears mainly in the nonsmokers and was perhaps masked in smokers.

Prevalence of bronchitis and shortness of breath increased from the pre-exposure baseline in the high exposure category, as measured by cumulative exposure, but these increases were not significant. As I have mentioned, about 4 percent of the population became acutely reactive or sensitized or susceptible or intolerant, which is in keeping with the limited data that are available on this in the world literature. You have to remember that in this situation, for the first time it was possible to get true incidence data, that is the appearance of sensitization. In the other limited studies that are available that was not possible because preexposure information was

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not available. Smoking and atrophy did not seem to be important predictors of whether or not somebody would become intolerant. As I have already suggested, some of these people have, so far, failed to obtain preexposure or presensitization expiratory flows. This is in keeping with the very latest reports a month or two ago at the American Thoracic meeting, from the Vancouver group on the western red cedar dust situation.

Although we did not feel justified in going above 0.02 parts per million in the bronchial provocation studies in the laboratory, we know that where this has been done, some people who are clinically intolerant to TDI vapor will respond not to 0.02 parts per million but to higher levels of exposure. Therefore, a negative challenge test at 0.02 parts per million does not necessarily mean the individual has not become reactive or intolerant. It just means that he is not reacting to that level. Again, there are ethical and perhaps even legal questions involved in exceeding the standard or TLV in the laboratory in exposure situations.

These last conclusions deal primarily with the immunology, which I have already indicated, the bottom line suggests that we still do not know. We think something is going on at the receptor level. Why some people have this abnormality and develop an inadequate response to stimuli to secrete cyclic AMP is not clear.

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DISCUSSION ON ISOCYANATE

QUESTION (Mr. Anderson): I am wondering if it is possible that there might be isocyanates in cigarette smoke that allow one to build up an immunity to isocyanates, like one can build up an immunity to arsenic by being exposed to low levels of arsenic?

ANSWER: (Dr. Weill): That is an interesting question. We came up with several possible explanations and that was not one of them.

Cigarette smoke is very complex; as all of you know, it contains many chemicals and particulates, Isocyanates do occur widely. For instance, of some interest to us was one of our individuals who became TDI reactive all of a sudden and could not tolerate one of his favorite foods, radishes. He developed severe bronchial spasm when he ate radishes. He ultimately lost his TDI sensitivity and then could eat radishes again. Radishes do contain an isocyanate. I do not know about cigarette smoke, but it is an interesting possibility.

QUESTION (Mr. Sales): All along we have been talking about rather stable minerals with long lifetimes, but isocyanates are noted for their reactivity. I wonder if the fact that these materials are active has been taken into account.

ANSWER (Dr. Weill): You are quite right. When TDI hits the moist bronchi mucosa, it does change; it is no longer in its chemical form and it is highly reactive. Something about either it or its transformation or its product produces the kinds of problems that I summarized.

We do have an interest in this. It is a very hard thing to get at. It would easily be studied in the animal model; unfortunately, so far there is no animal model for TDI asthma.

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