

Toluene Diisocyanate Exposure

Exposure Assessment and Development of Cross-Facility Similar Exposure Groups Among Toluene Diisocyanate Production Plants

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Objective: The objective of this study was to characterize workplace toluene diisocyanate (TDI) exposures using standardized industrial hygiene exposure assessment procedures for use in a prospective epidemiologic study of occupational asthma. **Methods:** Over 2300 representative routine full shift time-weighted average (TWA) and short-term high potential exposure tasks (HPETs) air samples in groups across three TDI plants were collected over a nearly 7-year period. **Results:** Data-derived similar exposure groups (SuperSEGs) were developed across the plants based on TWA sampling using cluster analysis. Individual cumulative exposure estimates were developed on the basis of the SuperSEGs. **Conclusion:** Workplace TWA exposures to TDI were adequately characterized quantitatively, but HPET exposures were adequately characterized only by qualitative measures. The mean TWA exposure was 0.65 parts per billion for 1594 routine samples. These TWA and HPET exposures can be used to support exposure-response analyses.

Isocyanates comprise a class of compounds that have at least one highly reactive -NCO group and include 2,4-toluene diisocyanate (TDI) and 2,6-TDI. Exposure to diisocyanates can cause adverse respiratory system effects, including respiratory tract irritation, sensitization, and asthma.¹⁻⁴ Many studies have shown that continued exposure to diisocyanates can lead to increasingly persistent and severe respiratory symptoms,⁵⁻⁸ and when a person has demonstrated any of these respiratory symptoms from exposure to diisocyanates, further contact with diisocyanates should be avoided.

Butcher⁹ and Diem et al¹⁰ reported anecdotal evidence from a 5-year study of workers in a TDI plant in which over half of the workers who developed asthma were exposed to high concentrations a short time before asthma occurred. A more recent study at a polyurethane foam plant characterized potential exposures using primarily area monitoring and found airborne TDI levels were low with more than 90% of fixed point air measurements below the detection limit.¹¹ Workers were assigned to high, medium, or low potential risk groups based on their primary work location and duties as well as input from an industrial hygienist (IH) who had

evaluated the plant. The authors found no significant associations between the assigned risk group and new asthma-like symptoms, new eye irritation, baseline lung function, change in lung function over the year of follow-up, or workers lost to follow-up. However, the prevalence of current asthma symptoms was significantly higher in the workers lost to follow-up than those who completed the 12-month follow-up. The authors concluded that their findings suggest possible early TDI-related health effects in a modern polyurethane production plant. Therefore, the relative contributions of lower-level and short-term higher-level TDI exposures to respiratory effects remain an open question, in part because few studies have incorporated collection and analysis of real-time industrial hygiene measurements or tracking of acute overexposure episodes.^{12,13}

PURPOSE OF THE OVERALL TDI STUDY

To address the relative contributions of lower-level and short-term higher-level TDI exposures to respiratory effects, collaborative research was initiated between the National Institute for Occupational Safety and Health (NIOSH), member companies of the American Chemistry Council (ACC) Diisocyanates Panel, and the International Chemical Workers Union (ICWU) to investigate the exposure conditions consistent with induction of respiratory sensitization. A prospective study was developed that followed a worker population potentially exposed to TDI in manufacturing facilities of U.S. TDI producers. Although the study began with six U.S. production plants, by the time the exposure data collection started, only three plants still produced TDI. The objective of the part of the study reported here was to characterize workplace TDI environmental concentrations based on the use of standardized industrial hygiene monitoring and exposure assessment procedures. The exposure assessments were conducted to support the evaluation of the hypotheses of whether:

- (1) The annual incidence of TDI-induced asthma in the TDI production environment was well under 1% provided TDI concentrations are maintained below recommendations [threshold limit values (TLVs)] by the American Conference of Governmental Industrial Hygienists (ACGIH) and a rigorous clinical work-up of potential cases is accomplished; and
- (2) In the TDI production environment with an active event reporting system and industrial hygiene program, the majority of work-related asthma cases were associated with nonroutine exposure episodes.

This paper characterizes the TDI time-weighted average (TWA) exposures and short-term exposures during tasks identified as having potential for high exposure or high potential exposure tasks (HPETs), and develops cross-facility similar exposure groups. (Note: In February 2016, after the study was complete, ACGIH lowered the recommended TLV-TWA for 2,4- or 2,6-TDI from 5 to 1 ppb and the TLV-STEL from 20 to 5 ppb. All references in this paper are to the adopted TDI TLV values that were in place before 2016, and not the TLVs adopted in 2016.) The cross-facility exposure groups and exposures are used in epidemiologic analyses reported elsewhere to test the hypotheses described above.

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Paul Middendorf, William Miller, and Brent Doney declare no conflicts of interest. Timothy Feeley is an employee of Covestro, one of the companies included in the study. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the NIOSH.

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DOI: 10.1097/JOM.0000000000001117

METHODS

The study was conducted under a protocol approved by the NIOSH and the Dow Chemical Company Institutional Review Boards. At the beginning of the study, 197 of the estimated 300 eligible workers (eligibility is defined in Reference ¹⁴) elected to participate in the study; however, these numbers fluctuated throughout the study, as new workers became eligible to participate in the study or previously enrolled workers declined to continue their participation in the study.

Exposure assessment was conducted at three locations: BASF in Geismar, Louisiana; Covestro LLC (formerly known as Bayer MaterialScience LLC) in Baytown, Texas; and Dow Chemical Company in Freeport, Texas. The plants were assigned arbitrary identifications as Plant 1, Plant 2, and Plant 3, and the specific locations were not identified in the analysis. A uniform exposure assessment strategy was developed by a team of IHS from NIOSH and from industry, which included development of plant-level similar exposure groups (Plant/SEGs), identification of HPETs, quantitative and qualitative exposure assessment, and the utilization of standardized sampling and analytical methods to provide the exposure data needed to achieve the study's aims.

Each TWA or HPET sample was collected from the worker's breathing zone and was documented on a standard form, the IH Monitoring Data Collection form, which identified the Plant and included information on the Plant/SEG, HPET, operating conditions (routine, upset, shutdown/turnaround, or start up), sample date, sample duration, sample result in parts per billion (ppb), the type of engineering controls in place, and the type of respiratory protection worn. The forms were submitted to a third-party vendor to process forms, anonymize the data, and input the data into a database. Continuous area monitoring of TDI was not available for this study.

Similar Exposure Groups and High Potential Exposure Tasks

SEGs are groupings of employees who perform similar tasks that produce similar worker exposures. The first part of the exposure assessment strategy was to develop plant-level similar exposure groups (Plant/SEGs). Plant/SEGs were initially developed by identifying job titles that were known to have potential exposures to TDI, based on prior experience. Worker groups within these job titles were further evaluated by IHS including two NIOSH IHS and at least one IH from the participating plant who was knowledgeable of the plant processes and operations. In assigning worker groups to Plant/SEGs, the IHS considered the tasks performed by each worker group and the likelihood of similar exposures based on their knowledge of the plant processes and operations. The group also identified HPETs for all workers performing tasks in areas with the potential for TDI exposure.

The TDI manufacturing processes are similar among the plants and consist of hydrogen and carbon monoxide generation, phosgene synthesis, toluene diamine (TDA) synthesis, TDI synthesis, and loading TDI product into railcars or trucks (TDI Loading); some plants also loaded TDI into drums (Drumming). In TDI production, the job tasks with potential or known exposure to TDI include production, maintenance, storage and transportation, housekeeping, incident response, and laboratory analysis of TDI process samples. Not all plants had each of the identified SEGs, and the same tasks were not always performed by workers in different plants with the same job titles. After the initial assignment of Plant/SEGs and HPETs, plant tours and systematic discussions of the TDI production and handling process flow and the roles of the defined SEGs in the process were conducted with the local and sometimes corporate IH staff. The discussions led to the determination that the SEGs defined by job title adequately characterized the potential TDI exposure in these operations. After the plant tours and the discussions, the following Plant/SEGs were identified:

- TDI loading/Shipping personnel;
- Drumming personnel;
- Field unit operators;
- Process chemist;
- Engineers/Plant supervision;
- Laboratory personnel;
- Instrument technicians;
- Control room operators;
- Shift supervisors/Foremen; and
- Maintenance [in TDI production units].

In addition to the SEGs, tasks that had the potential for short-term, high exposures were identified. These HPETs were primarily characterized by handling TDI outside the usually totally enclosed processes. The list of HPETs was refined and confirmed in discussions of the production processes and HPETs during the plant tours. After the plant tours and the discussions, the following plant HPETs were identified:

- Equipment drain/Decontamination;
- Line opening;
- Process sampling;
- Waste handling;
- Hot work (such as, welding, cutting, and grinding);
- Confined space work;
- TDI loading;
- System upset/Area exposure; and
- Emergency response.

Exposure Assessment

Strategy

An initial strategy to collect full-shift personal samples (TWA samples) was developed and explained to the personnel responsible for implementing the sampling plans at each plant. The strategy specified quarterly sample collection throughout the calendar year of at least six samples of randomly selected members of each Plant/SEG, or all the SEG members if there were fewer than six members. The number of exposure samples could be reduced by half after the first year if the mean TWA exposure for an SEG was less than half of the TLV-TWA (5 ppb). However, the fully randomized sample collection strategy was not conducted at the plants and the number and timing of samples collected were determined at each plant on the basis of local factors that varied among the plants. In an effort to comply with protocol sample collection requirements, the number of TWA and HPET samples collected at each plant was tracked through quarterly submittal of a summary sheet. The number of TWA and HPET samples collected at each plant was compared with the number required by the protocol. When short-falls were noted in Plant/SEGs and/or HPET samples, recommendations were made to increase sample collection in the next quarter.

All employees in an SEG were eligible for sampling whether or not they participated in the medical monitoring part of the study, and the employee monitored on a given day was to be determined randomly, not arbitrarily, from among the employees available. However, compliance with this requirement for random sampling was not assessed. Contractors were not included in the SEG and were not eligible for sampling. In addition to the quantitative exposure assessment, qualitative exposure information was collected for each plant-level HPET. Each year, the plants were instructed to submit an estimate of the annual frequency that each HPET was performed by members of each Plant/SEG.

Dermal Exposure

Although TDI is a recognized sensitizer after dermal absorption in the workplace, no attempt was made to characterize dermal

exposure among the workers. This important route of exposure was not included in the study protocol because a standard method to assess dermal exposure was not available and dermal exposure was expected to occur sporadically which would limit the ability to include it in the analyses in a rigorous way. At the time the protocol was being developed, biomonitoring for TDI exposure was also considered but not included in the protocol because a validated method was not available.

Air Sampling

Air samples representing shift length duration TWA exposures and exposures during the defined HPETs were collected. Shift lengths varied between Plant/SEGs; some were 8 hours, and some were 12 hours. For TWA exposures, multiple samples collected on the same individual on the same day were combined to estimate the full-shift TWA. Air samples were collected with calibrated personal sampling pumps using the Covestro Industrial Hygiene Laboratory Method 1.19.0, which is equivalent to the OSHA 42 Method¹⁵ for measuring airborne personal exposures to TDI. However, the Covestro method uses a smaller diameter filter (13 mm) and additional reagent is used on the glass fiber filter to allow for sampling up to 4 hours and use in higher humidity environments.

Sample media for all three participating plants was prepared at the Covestro Industrial Hygiene Laboratory in Pittsburgh, Pennsylvania (Laboratory). Cassettes with 13 mm glass fiber media were treated with 1-(2-pyridyl)piperazine when requested from a plant because, once prepared, the filters were to be used within 2 weeks to ensure adequate collection efficiency. Upon completion of sampling at the plants, the samples were sent to NIOSH and relabeled to blind the laboratory and then sent to the Covestro lab for analysis. For quality assurance, spiked quality control samples were also sent from NIOSH to the Covestro laboratory for analysis. Feedback on the quality control results was provided to the laboratory. The samples were analyzed for both 2,4-TDI and 2,6-TDI, and exposure concentrations were calculated. The Laboratory reported either the quantitative result when it was greater than the limit of quantitation (LOQ) or the LOQ for the sample; results between the limit of detection and the LOQ were not provided. Therefore, for purposes of the study, sample results that were reported as less than the LOQ were assigned a value of one-half the LOQ for the sample. The results for 2,4-TDI and 2,6-TDI were added to give the total TDI exposure. Only the total TDI exposures are reported and used. For TWA exposures, when the sample duration was less than the work shift, the samples collected were assumed to represent the entire work shift. For HPET samples, sample durations less than 15 minutes were assumed to have zero exposure for unsampled time.

Replicate Samples

Samples collected within the same Plant/SEG on the same date were considered replicate samples. The median values of subsamples (ie, samples from the same plant, SEG, and sampling date) were calculated, reported, and used in analyses. Otherwise, all available samples were included in each statistical analysis.

Operating Conditions

Each of the collected TWA and HPET samples was classified as “routine,” “turnaround,” “shutdown,” or “upset” on the basis of the operating conditions. Very few of the samples were collected during “turnaround,” “shutdown,” or “upset” conditions, and the types of HPETs were expected to vary between Plant/SEGs, so cross-facility analyses using TWA and HPET samples were restricted to “routine” samples. Also, additional analysis, not shown here, indicated that the addition of the other samples had a little impact on the results for the modeling and for the calculation of the 95th percentiles.

Respirator-Adjusted Exposures

Each of the three plants had standard operating procedures that specified the type of respirator that was to be worn during specific jobs (TWA) or during specific tasks, such as HPETs. However, several submitted IH Monitoring Data Collection forms indicated that a different type of respirator had been worn other than that specified in the standard operating procedures.

Estimates of the workers' respirator-adjusted exposures were developed using the submitted IH Monitoring Data Collection forms. When the form indicated that a respirator had been worn by the worker while the sample was collected, the sample result was divided by the assigned protection factor (APF) for that type of respirator.¹⁶ An APF of 10 was used for tight-fitting half-mask respirators; an APF of 50 was used for full-face tight-fitting respirators; and because the information did not differentiate between supplied air and self-contained breathing apparatus, an APF of 2000 was used for all types of supplied air respirators because full-face supplied air respirators were used. When the sample results for either or both 2,4- or 2,6-TDI were less than the LOQ, the resulting estimated total TDI exposure was adjusted by dividing the exposure by the APF for the respirator identified to calculate the respirator-adjusted exposure. These calculated exposures are referred to as “respirator-adjusted” exposures. When the respirator information was missing, we assumed that no respirator was worn, and the respirator-adjusted exposure was the same as the nonadjusted exposure.

Questionnaires and Forms

A registration form was completed for all potential participants in the study and included the original hire date, first day in job with potential TDI exposure, a requirement to select at least one SEG in which they worked, and an option to select up to two SEGs (the percentage of time performing the SEG was also captured). Other questionnaires used in this study were a Periodic Questionnaire administered to the workers immediately after study registration and at each annual medical visit to capture information about change in job (SEG and HPETs). There was also an Intake Questionnaire administered within 6 months of registration. The participants were asked in the Periodic and Intake Questionnaires if “During the last 12 months, have you... Noticed an odor of TDI in your work area?” or “Been in the area of a release of TDI, such as from a leaky valve or spill?” If they had, for each question, they were asked to quantify how often with choices of “1–3 times,” “4–11 times,” “At least once a month,” or “At least once a week.” If an event or medical finding indicated that the participant needed further evaluation, a Second Tier Questionnaire asked the same and additional questions to determine whether a clinical evaluation was needed.

In the event a participant experienced an acute inhalation event where a chemical was released, the Acute Inhalation Worksheet was used to capture information about the event, including the SEG, HPETs, and chemical(s) released, including TDI and/or chemicals such as phosgene, hydrogen chloride, and chlorine. Additional details regarding the questionnaires and forms used for this study are discussed in the study by Cassidy et al.¹⁴

Cross-Facility SEGs (SuperSEGs)

TWA Exposures

The original intent of the study was to combine Plant/SEGs with the same name across plants to uniformly characterize the exposure groups in the study. However, the differences in the geometric means between some were relatively large and did not meet the criterion specified in the protocol of combining SEGs with geometric means that were different by no more than a factor of two. Therefore, a method was developed to combine Plant/SEGs, which had been determined using job titles and professional judgment into data-derived cross-facility SEGs (SuperSEGs) that are comprised of

one or more Plant/SEGs. Advantages of developing SuperSEGs are that they helped to protect the identity of persons participating in the study and they potentially could improve the power of the study by increasing the number of persons in each SEG. Although combining the Plant/SEGs into SuperSEGs could potentially increase bias if the exposures between the Plant/SEGs are different, it was determined that the advantages were more important than the potential disadvantage.

To develop the SuperSEGs, the TWA exposure results, without regard to the use of respirators for each Plant/SEG, were categorized into one of the following five groups: less than 0.1 ppb; 0.1 to less than 0.5 ppb; 0.5 to less than 2 ppb; 2 to less than 5 ppb; and at least 5 ppb. The bounding categories (<0.1 and ≥ 5 ppb) were chosen because 0.1 ppb is approximately the LOQ, and 5 ppb was the 8-hour TWA-TLV at the time of this study. The intermediate categories were chosen to differentiate between modes that were identified while investigating the structure of the data.

Cluster analysis was performed on all of the Plant/SEGs by adapting the methods given,^{17,18} which are applied to the rows of a contingency table where the columns are defined by the five exposure categories above. This approach is less dependent on the scaling of the data than when using continuous outcomes, which can sometimes distort the results of a cluster analysis.¹⁹ The clustering methods rely on a distance measure based on the Chi-square statistic. Greenacre²⁰ has also shown that the Chi-square distance is a type of “Mahalanobis distance,” a widely used distance measure in multivariate analysis that weights the Euclidean distance using a covariance matrix. However, the typical application of the Mahalanobis distance is based on the distance between pairs of observations. The Chi-square distance is defined for the distance between two samples while using the associated covariance, which follows the track suggested by Kendall.²¹ A possible drawback to using the Chi-square distance is that a row containing a small number of counts can, in some cases, act as an outlier and overly influence the formation of clusters.

As recommended by Greenacre,¹⁷ Ward minimum-variance method of clustering is applied to the Chi-square distances that are calculated using the frequencies for the five exposure categories defined above, and the results of the cluster analysis are presented in a cluster tree (also called a dendrogram), which indicates the stages at which rows or groups of rows (in this case Plant/SEGs) are merged. Although the methods are otherwise identical, Greenacre expresses his results in terms of the Chi-square scale, whereas the scale for the results here are expressed in terms of the between sum-of-squares that are calculated from Ward method.

Respirator-Adjusted SuperSEGs (RA-SuperSEGs)

Cross-facility SuperSEGs were also developed on the basis of the respirator-adjusted TWA exposures. Adjusting exposures to account for the use of respirators often produced estimates that are several orders of magnitude below the TLV-TWA, and their biological relevance is unknown. Several cut points for developing the RA-SuperSEGs were considered. Choosing cut points at or near the TLV would have produced categories with very few exposures, and choosing cut points at very low exposures would have produced exposure categories with little difference related to health outcomes. After considering the need to have categories with enough exposures to develop stable SuperSEGs and the preference to have the categories relevant to known health outcomes, it was decided to develop two categories with a cut point at 0.5 ppb. The resulting categories of exposure are less than 0.5 and at least 0.5 ppb. Development of the RA-SuperSEGs then followed the same procedures as were described above for unadjusted TWA exposures.

Contrast Statistic

To provide an estimate of how distinctive the SuperSEGs are, a contrast statistic was calculated using the formula: Contrast = between

SuperSEG variance/(between SuperSEG variance + within SuperSEG variance) for the TWA exposures. The method for calculating the contrast statistic was adapted from the method of Kromhout and Heederik.²² They define individual workers as their sampling units, but for this analysis, the sampling units were the Plant/SEG/sampling date combinations, which were nested within the Plant/SEG combinations, which in turn were nested within the SuperSEGs. For the respirator-adjusted exposure outcomes, the respirator-category variable entered a mixed model as a fixed effect in the calculation of the variance components for the contrast statistic.

Peak Exposures

HPET samples were collected for the duration of the task because of the potential to disrupt the process and the difficulty of replacing sampling media at specific intervals. Therefore, the HPET results are appropriately described as task exposures. For the purposes of this study, the HPET exposures are compared to the 15-minute TLV-STELTM [short-term exposure limit (STEL)] at the time of this study. For HPETs that lasted less than 15 minutes, zero exposure was assumed for the unsampled period. For HPETs that lasted longer than 15 minutes, if the HPET exposure result exceeded the STEL, then for at least some 15-minute time period during the sampled HPET, the STEL was exceeded. However, for the HPET exposures lasting longer than 15 minutes that did not exceed the STEL, it is possible that during some 15-minute period the STEL was exceeded, but is not identified. Therefore, the number of HPET exposures reported here as exceeding the STEL is the minimum number of HPETs that exceeded the STEL. For each Plant/SEG, an estimate of the number of HPETs that were conducted during the study and exceeded the TLV-STEL was calculated by:

- (1) multiplying the annual estimate of the number of each type of HPET conducted by the % of the HPET samples for that HPET that exceeded the STEL, and
- (2) summing over all of the types of HPETs conducted in that SEG to get the total number of HPETs conducted by the SEG that exceeded the STEL.

Other researchers, such as Smith and Kriebel,²³ have suggested alternative methods for measuring peak exposures, such as the estimated 95th percentile. Therefore, we also calculated the 95th percentile of the TWA exposures for each of the Plant/SEG combinations. For this estimate, we assumed a lognormal distribution and used a maximum-likelihood approach for a censored regression model, which is also sometimes described as a type of Tobit model.²⁴ Hewett and Ganser²⁵ have shown that maximum-likelihood estimators are generally less biased for estimating the 95th percentile of a lognormal distribution. The bias is generally much less for the estimation of means and, therefore, the simpler approach of assigning half the LOQ to the censored data was maintained for the other reported statistics.

Cumulative Exposures

Cumulative TWA exposure estimates for individuals were developed on the basis of the quantitative exposures. The TWA exposure data generally followed a log-normal distribution. For log-normal data, where $x = \ln(y)$, the mean exposure μ_y is estimated using the following equation:

$$\mu_y = e^{\mu_x + \sigma_x^2/2}$$

The resulting means for the TWA exposure clusters were then used in the calculations of the cumulative TWA exposures.

Because detailed work-histories were not available, worker reports collected from the Initial and Periodic Questionnaires were used to estimate cumulative exposures. About one-quarter of the

TABLE 1. Distribution of TWA and Respirator-Adjusted TWA Exposures by Plant and SEG

Plant	SEG	Total	TWA Range, ppb					Overall	RA-TWA Range, ppb						
			<0.1	0.1–0.5	0.5–2	2-5	≥5		<0.5	≥0.5	Overall				
1	Field Operator	120	77	26	11	3	3	0.03	—	19.1	112	8	<0.001	—	5.58
	Loading	116	52	15	22	17	10	0.03	—	92.2	105	11	<0.001	—	6.72
	Laboratory	101	76	20	3	0	2	0.03	—	12.4	96	5	0.03	—	12.4
	Instrument Tech	95	73	14	6	2	0	0.02	—	3.16	90	5	<0.001	—	2.03
	Shift Supervisor	100	90	8	2	0	0	0.03	—	1.23	98	2	<0.001	—	1.23
	Engineer Support	90	88	1	1	0	0	0.03	—	2.52	88	2	0.03	—	2.52
	Total	622	456	83	45	23	15	0.02	—	92.2	589	33	<0.001	—	12.4
2	Field Operator	44	40	2	0	1	1	0.01	—	9.21	44	0	<0.001	—	0.10
	Loading	49	30	10	7	2	0	0.01	—	2.42	49	0	<0.001	—	0.17
	Laboratory	10	9	1	0	0	0	0.01	—	0.16	10	0	<0.001	—	0.16
	Instrument Tech	38	38	0	0	0	0	0.01	—	0.08	38	0	<0.001	—	0.035
	Maintenance	43	41	1	1	0	0	0.01	—	1.07	43	0	<0.001	—	0.085
	Engineer Support	35	35	0	0	0	0	0.01	—	0.042	35	0	0.01	—	0.042
	Control Rm Op	36	36	0	0	0	0	0.01	—	0.065	36	0	<0.001	—	0.065
	Process Chemist	10	10	0	0	0	0	0.01	—	0.055	10	0	0.01	—	0.055
	Drumming	16	8	6	1	1	0	0.03	—	3.69	16	0	<0.001	—	0.025
	Technician	40	39	1	0	0	0	0.01	—	0.15	40	0	<0.001	—	0.095
	Total	321	286	21	9	4	1	0.01	—	9.21	321	0	<0.001	—	0.17
3	Field operator	109	58	28	10	4	9	0.02	—	90.0	109	0	<0.001	—	0.41
	Loading	98	19	32	34	9	4	0.03	—	15.3	94	4	<0.001	—	3.16
	Laboratory	103	96	5	1	1	0	0.02	—	2.24	101	2	0.02	—	2.24
	Instrument tech	79	59	18	0	1	1	0.02	—	11.6	77	2	<0.001	—	11.6
	Shift supervisor	90	78	11	1	0	0	0.02	—	0.51	89	1	<0.001	—	0.51
	Maintenance	50	31	12	7	0	0	0.02	—	1.61	46	4	<0.001	—	1.61
	Control Rm Op	95	87	5	2	0	1	0.02	—	5.57	92	3	0.02	—	5.57
	Drumming	27	2	6	8	7	4	0.03	—	32.7	13	14	<0.001	—	32.7
	Total	651	430	117	63	22	19	0.02	—	90.0	621	30	<0.001	—	32.7

workers stated their first date they were in a job with potential TDI exposure. For the other workers, the potential exposure was assumed to commence with the beginning of study when the hire-date preceded the start of the study, or was assumed to begin at their hire-date when this occurred after the start of the study. Other assumptions about the beginning of exposure potential for calculating cumulative exposures, such as assuming that potential exposures began at hire-dates before the start of the study, were investigated and found to be less useful for modeling the health outcomes.

Cumulative HPET exposures were determined as the number of HPET exposures that exceeded the STEL as described above. It is also possible to use the estimated 95th percentiles for the TWA exposures as an index for the peak exposures instead of the HPET cumulative exposures. The 95th percentile does not require the tenure in each Plant/SEG and so relies much less on the validity of the work-history information. The 95th percentile for the TWA was determined for each worker by assigning that worker's highest estimate of the 95th percentile among the Plant/SEGs in which the worker was employed. This metric had a rank correlation greater than 0.8 with the estimated HPET cumulative exposure.

All statistical analyses were performed using SAS software (SAS Institute, Cary, NC). A macro that performs the cluster analysis is available upon request from the authors.

RESULTS

Sampling for TWA and HPET exposures began in 2006 and ended in 2012. After excluding nonroutine samples (*n* = 105) and using the median of the samples for any Plant/SEG/sampling date combinations with multiple samples as a single representative sample for that day, 1594 TWA samples and 755 HPET results were available for analysis. For 962 (60.4%) of the TWA samples, the results for both 2,4- and 2,6-TDI were less than the LOQ. Also, for 1170 (73.4%) of the TWA samples, the result of either 2,4- or

2,6-TDI was less than the LOQ. For 455 (60.3%) of the HPET samples, the results for both 2,4- and 2,6-TDI were less than the LOQ. Also, for 531 (70.3%) of the HPET samples, the result of either 2,4- or 2,6-TDI was less than the LOQ. More TWA samples were collected in the period from 2006 to 2009 (*n* = 1092) than from 2010 to 2012 (*n* = 502) in part because one of the plants discontinued exposure data collection when TDI production ceased. Also, one of the plants emphasized collecting HPET samples during the second period at the expense of collecting TWA samples. The arithmetic mean for all TWA exposures was 0.65 ppb, and the TWA exposures ranged from an estimated 0.01 ppb to a measured 92 ppb. The sampled period for the TWA exposures on average included 93.3% (S.D. = 7.3%) of the work period.

TWAs

The Plant/SEG TWA exposure distributions among the categories for unadjusted and respirator-adjusted exposures are provided in Table 1. After applying the clustering methods of Greenacre^{17,18} to the exposure profiles, the cluster tree in Fig. 1 was produced for the TWA exposures. Moving from left to right in the figure, the vertical line-segments indicate the between-cluster sum of squares at which the Plant/SEGs or groups of Plant/SEGs were merged. For example, except for “Drumming” and “Loading,” all of the Plant 2 SEGs were combined during an early stage of the clustering procedure. An examination of the cluster tree led to the development of five clusters of Plant/SEGs, which are denoted as “SuperSEGs.” The geometric means and geometric standard deviations for the SuperSEGs, as well as their Plant/SEG members, are summarized in Table 2. Also provided in Table 2 are the estimates of the 95th percentile for each Plant/SEG. As Fig. 1 and Table 2 show, exposure geometric means of the SuperSEGs increase with the SuperSEG number, and the SuperSEG with the highest geometric mean exposure contains only one Plant/SEG.

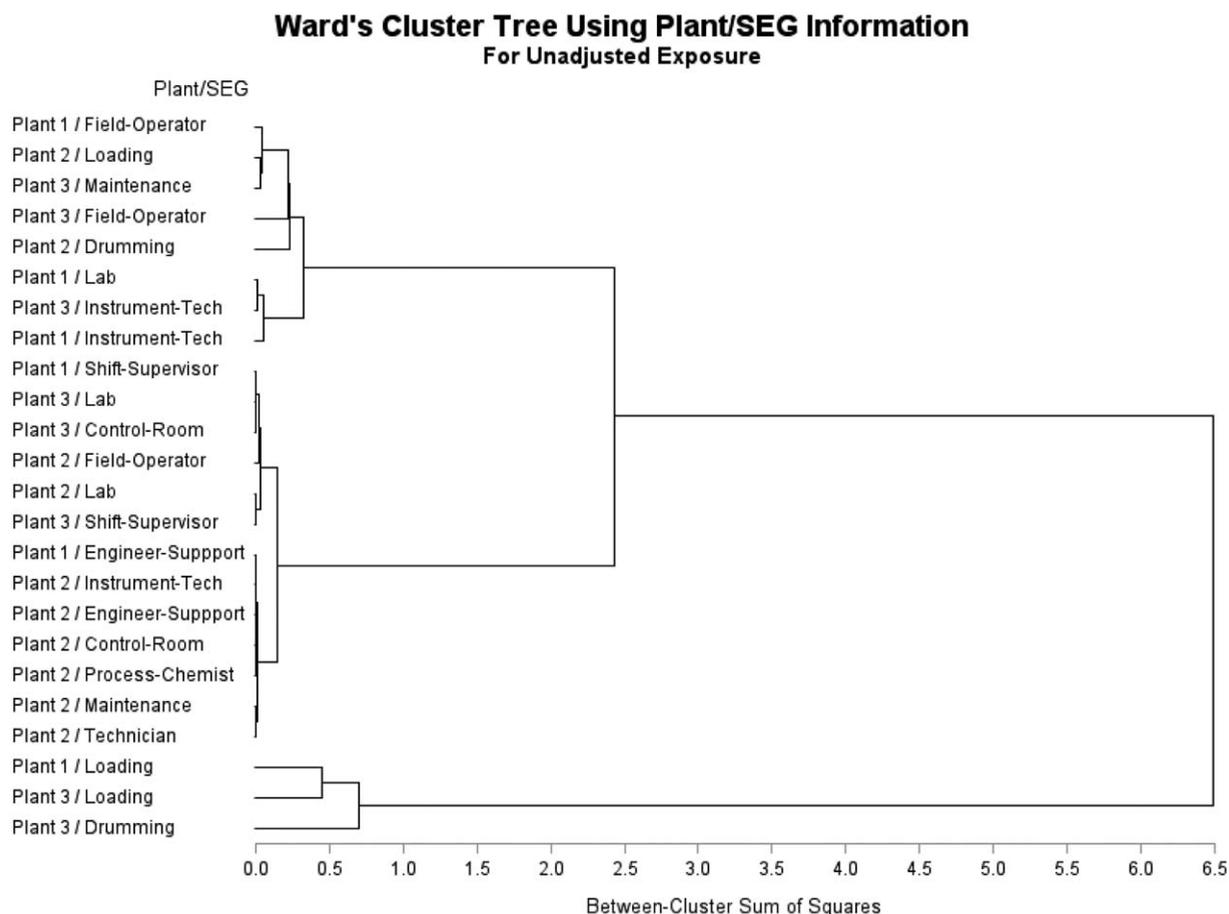


FIGURE 1. Clustering of Plant/SEGs into cross-facility SEGs (SuperSEGs) based on TWA exposures.

Figure 2 shows the cluster tree for the respirator-adjusted exposures. Note that in Figs. 1 and 2, the clusters are differentiated at a threshold in the range of 0.3 to 0.5 for the between-cluster sum-of-squares.

The methods of Kromhout and Heederik²² were adapted to produce the results in Table 3. The “*n*” in parenthesis indicates the number of groups or clusters used in the calculation of a contrast statistic. In the last row (labeled “Overall”), “*n*” represents either the total number of Plant/SEG combinations or the total number of SuperSEGs. Also shown is the $BGR_{.95}$ statistic, which estimates the ratio of the 97.5th and 2.5th percentiles of the between-group distribution and so indicates the range of measured exposures. The contrast statistic indicates the discrimination provided by the clustering. In the “Contrast” columns, the contrast statistics for the original Plant/SEG groupings and values for the SuperSEGs are presented for both the unadjusted exposure outcomes and the respirator-adjusted outcomes. Because all the Plant/SEG combinations for Plant 2 were assigned to the same respirator-adjusted SuperSEG, there was no estimate of the between-group variance component and, hence, no contrast estimate was available for the respirator-adjusted exposures for Plant 2. The comparison of the contrast statistics indicates that discrimination is improved overall by using the SuperSEG grouping for either the unadjusted or respirator-adjusted exposures. For the unadjusted exposures, the improvement is greater for Plant 2 than for Plants 1 and 3, which have larger estimated ranges of exposures.

After applying the clustering methods of Greenacre^{17,18} to the respirator-adjusted exposure profiles, the cluster tree in Fig. 2

was produced. Using a similar between-cluster sum of squares in the range of 0.3 to 0.5 as the basis for differentiating between clusters, three RA-SuperSEGs were identified. However, most of the Plant/SEGs are included in RA-SuperSEG 1, only three Plant/SEGs are included in RA-SuperSEG 2, and one Plant/SEG is included in RA-SuperSEG 3. Thus, the respirator-adjusted TWA exposures do not differentiate many exposure groups. The geometric means and geometric standard deviations for the RA-SuperSEGs, as well as their Plant/SEG members, are summarized in Table 2. The respirator adjustment of exposures often produced a bimodal distribution within the Plant/SEGs because some of the exposures were adjusted by the APF while other exposures were not. For the Plant/SEGs with a bimodal distribution, the geometric standard deviations were not calculated for these Plant/SEGs because the assumption of log-normality was not met.

Cumulative Exposures

The number of workers in the study within specified ranges of estimated cumulative exposures (ppb-years) for the unadjusted and respirator-adjusted cumulative exposures is provided in Fig. 3. When the estimated cumulative exposures are adjusted for respirator use, they provide substantially lower estimates of cumulative exposure, and only one worker was estimated to have a respirator-adjusted cumulative exposure greater than 5 ppb-years.

HPETs

The estimate of the total number of HPETs that exceeded the STEL during the study is provided for each Plant/SEG in Table 4.

TABLE 2. TWA Exposures by Plant/SEGs, SuperSEGs, and RA-SuperSEGs

SuperSEG	GM ^a , ppb	GSD ^b	Plant 1				Plant 2				Plant 3						
			SEG	N	GM, ppb	GSD	95%ile TWA ^c	SEG	N	GM, ppb	GSD	95%ile TWA	SEG	N	GM, ppb	GSD	95%ile TWA
1	0.035	2.09	Engineer support	90	0.036	1.88	0.01	Instrument tech	38	0.025	1.62	0.20	Laboratory	103	0.038	1.94	0.09
			Shift supervisor	100	0.042	2.07	0.23	Engineer support	35	0.026	1.40	0.20	Control Rm Op	95	0.039	2.27	0.26
								Control Rm op	36	0.025	1.55	0.20	Shift supervisor	90	0.043	2.02	0.23
								Process chemist	10	0.027	1.54	0.20					
								Technician	40	0.026	1.66	0.18					
								Laboratory	10	0.029	2.05	0.23					
								Maintenance	43	0.034	2.31	0.16					
2	0.062	3.03	Instrument tech	95	0.064	3.14	0.77	Field operator	44	0.042	3.51	0.34	Instrument Tech	79	0.052	2.96	0.42
			Laboratory	101	0.069	2.97	0.64										
3	0.108	5.14	Field operator	120	0.094	4.41	2.00	Loading	49	0.089	4.58	1.52	Maintenance	50	0.083	3.72	0.85
4	0.343	6.84	Loading	116	0.29	8.90	19.2	Drumming	16	0.12	4.53	1.69	Field Operator	109	0.15	6.97	7.07
5	1.08	4.67											Loading	98	0.43	4.64	4.36
													Drumming	27	1.08	4.67	12.11
RA-SuperSEG																	
1	0.009		Engineer support	90	0.036	1.89		Instrument Tech	38	0.002	—		Control Rm Op	95	0.039	2.27	
			Instrument tech	95	0.023	—		Engineer Support	35	0.026	1.40		Field Operator	109	0.001	—	
			Shift supervisor	100	0.035	—		Control Rm Op	36	0.020	—		Laboratory	103	0.038	1.94	
			Laboratory	101	0.069	2.97		Process chemist	10	0.027	1.54		Loading	98	0.001	—	
								Technician	40	0.010	—		Shift Supervisor	90	0.030	—	
								Maintenance	43	0.0003	—		Instrument Tech	79	0.039	—	
								Field operator	44	0.00004	—						
								Loading	49	0.00005	—						
								Drumming	16	0.0005	—						
								Laboratory	10	0.029	2.05						
2	0.004		Loading	116	0.001	—						Maintenance	50	0.005	—		
			Field operator	120	0.009	—											
3	0.265											Drumming	27	0.265	—		

GM, geometric mean; GSD, geometric standard deviation; ppb, parts per billion; RA, respiratory-adjusted; SEG, similar exposure groups; TWA, time-weighted average.
^aGeometric mean of TWA exposures.
^bGeometric standard deviation of TWA exposures; Respirator-adjusted GSDs for SEGs with mixed respirator usage are not reported.
^cCalculated 95th percentile of the TWA distribution.

Several Plant/SEGs did not have any HPETs. The estimate of the total number of HPETs that exceeded the STELs generally increased as the TWA for the SuperSEG increased.

Exposure Information From Worker Questionnaires

Some exposure information was collected from questionnaires administered to workers. Both the Periodic and the Intake questionnaires asked, “During the past 12 months, have you noticed an odor of TDI in your work area? If ‘Yes’ please mark how often you had it in the last 12 months, 1–3 times; 4–11 times; at least once a month; at least once a week.” Of the 179 workers who completed Periodic Questionnaires, 118 or about two-thirds reported that they noticed the presence of TDI odors. The odor threshold for 2,4-TDI has been reported in the range of 0.17 ppm,²⁶ which is 8.5 times greater than the STEL, to 3.2 ppm,²⁷ which is 160 times greater than the STEL.

Respiratory Protection

The respirator used by the worker was recorded on the IH Monitoring Data Collection form when exposure results were submitted for inclusion in the database. The reported use of respiratory protection is provided in Table 5 for TWA and HPET exposures. The reports indicate that for most of the Plant/SEGs, workers did not commonly wear a respirator. The exceptions were the Field Operators and Loading SEGs in Plants 2 and 3, and Loading in Plant 1, who most commonly wore supplied air respirators.

For HPET exposures, the reports indicate that supplied air respirators were the most commonly used type of respiratory protection by each Plant/SEG, except for Laboratory workers in Plants 1 and 3, Technicians in Plant 2, and Maintenance workers in Plant 3. These workers most commonly wore no respiratory protection.

DISCUSSION

This prospective epidemiologic study of the primary producers of TDI in the U.S. required characterization of exposure. To that end, IHs from the companies involved in the study and from NIOSH worked together on the development and execution of the study. Plant visits by NIOSH were conducted to understand the processes, job descriptions, and tasks that involved exposure to TDI and to explore the sampling challenges.

The initial protocol called for first the assessment and then use of a TDI badge system, which would have been more convenient for the plants to use and might have increased compliance with the sampling strategy. This is particularly applicable to the HPET samples that were mostly of short duration, occurred unpredictably, and required detailed coordination between process personnel and IH personnel at the plant. However, the badge system was not able to be validated at the ambient concentrations needed for the study. Therefore, a validated sampling method that required the use of sampling pumps and prepared media with a limited shelf life was selected because it had an adequate LOQ for the study. As a result, the TWA exposures at the plants were adequately characterized, but the HPET sample collection was limited and sporadic. Some of the HPET exposures identified during the plant visits and included in the protocol were not sampled. The lack of uniform sampling minimized our ability to analyze and interpret the HPET data.

The study originally included six plants, but at beginning of data collection, only three plants were in TDI production. The ability to characterize exposure at these three plants was limited by the shutdown of TDI production at one plant midway through the study and the difficulty capturing HPETs and anything other than routine operations.

The unadjusted exposure represents exposures in the breathing zone. However, approximately two-thirds of the samples were

Ward's Cluster Tree Using Plant/SEG Information For Respirator-Adjusted Exposure

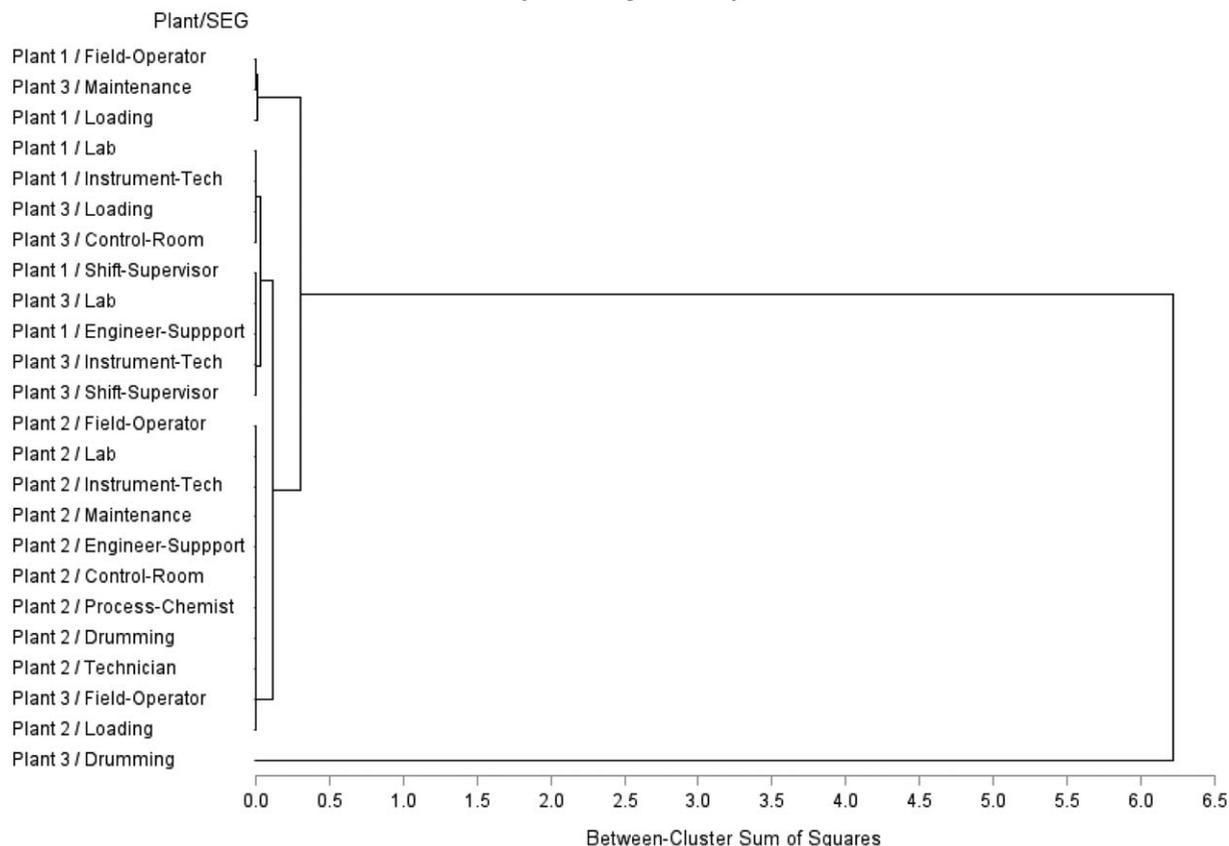


FIGURE 2. Clustering of Plant/SEGs into cross-facility SEGs (RA-SuperSEGs) based on respirator-adjusted TWA exposures.

below the LOQ, which resulted in estimating the concentration at half the sample's reported LOQ. This introduces uncertainty into the reported exposures and the subsequent analyses.

As Table 2 indicates, some Plant/SEGs did not wear respirators during TWA samples, and there is no change between their unadjusted and respirator-adjusted exposures. However, other Plant/SEGs had substantial changes in their exposures after the adjustment for wearing a respirator, and in these cases, the large differences in the sizes of the adjustments introduce multiple modes into the exposure distributions. Although it is possible to calculate statistics, such as GSDs, for respirator-adjusted exposures, they

involve different methods and assumptions than for the unadjusted statistics that are reported in Table 2. Also, an interpretation of results will be complicated by the fact that the low levels of respirator-adjusted exposures are the result of two qualitatively different types of exposures: (1) low unadjusted exposures and (2) high unadjusted exposures that are subsequently respirator-adjusted. Therefore, any model that is then used to predict exposure will need to consider the separate contributions of the unadjusted exposures and the respirator use.

The original intent of the study was to combine SEGs with the same name across plants to uniformly characterize the exposure

TABLE 3. Contrast Statistics for TWA and Respirator-Adjusted TWA Exposures

	TWA Exposures			Respirator-Adjusted Exposures		
	BGR ₉₅	Plant/SEG	SuperSEG	BGR ₉₅	Plant/SEG	RA-SuperSEG
		Contrast	Contrast		Contrast	Contrast
Plant 1	~81	0.327 (n = 6)	0.357 (n = 4)	~52	0.165 (n = 6)	0.181 (n = 2)
Plant 2	~6	0.478 (n = 10)	0.718 (n = 2)	~2	0.342 (n = 10)	N/A (n = 1)
Plant 3	~16	0.682 (n = 8)	0.708 (n = 5)	~12	0.493 (n = 8)	0.638 (n = 3)
Overall	~21	0.557 (n = 24)	0.618 (n = 5)	~16	0.388 (n = 24)	0.402 (n = 3)

Number of groups used in a calculation is indicated in parentheses.

BGR₉₅, ratio of the 97.5th and 2.5th percentiles of the between-group distribution; RA, respiratory-adjusted; SEG, similar exposure groups; TWA, time-weighted average.

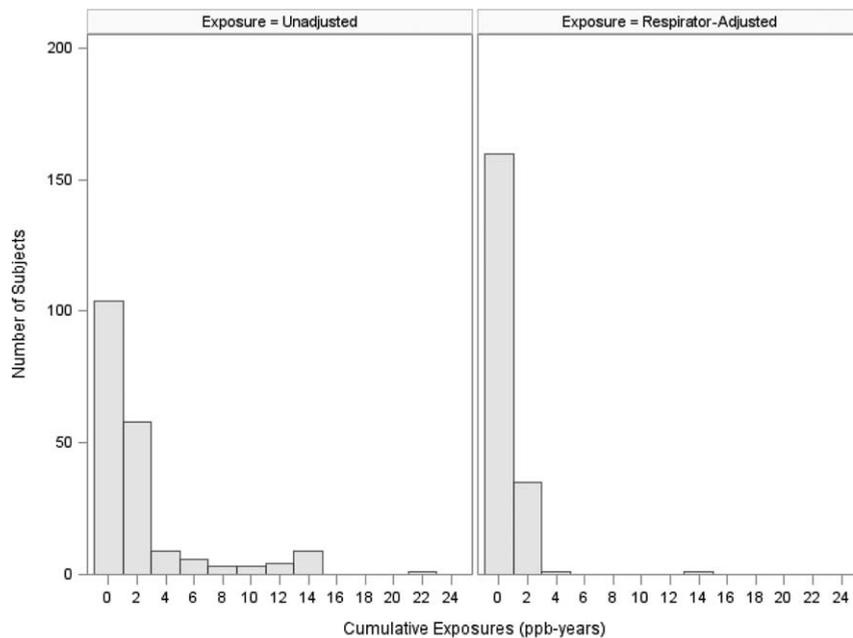


FIGURE 3. The frequencies of the estimated cumulative exposures (ppb-years) for the unadjusted and respirator-adjusted exposures of the 197 workers who participated in the study.

groups in the study. However, the differences in the geometric means between some were relatively large and did not meet the criterion specified in the protocol of combining SEGs with geometric means that were different by no more than a factor of two. It was observed that the exposures in the Plant 2 SEGs were frequently substantially less than exposures in the same named Plant/SEG in the other plants, for example, the Field Operators had a wide range of exposures, and the geometric mean for Plant 1 was more than twice that of Plant 2. One explanation for the differences found for Plant 2 is that the exposure sampling indicated that engineering controls were involved in about 50% of the samples, whereas this was true for less than 5% of the samples for the other two plants. Therefore, ways to combine across facilities without regard to the name of the SEGs were investigated. This resulted in the

development of the SuperSEG concept described previously, and SuperSEGs were developed on the basis of TWA exposures.

The cumulative exposure metric was developed to better understand the relationship between the induction of asthma and long-term exposures. Cumulative exposure is most appropriate to use when a unit of dose increases the risk of tissue or cell injury by a constant amount, and the risk is independent of the pattern of intensity and the duration of exposure, and the total dose is the most important exposure-related determinant of disease risk. However, if the risk of disease is dependent on the interplay between intensity and duration of exposure, the cumulative exposure would not be an appropriate metric to use in modeling the exposure–disease relationship.^{28,29} Two alternative metrics were developed to explore the relationship between asthma induction and short-term

TABLE 4. HPET Exposures by Plant/SEG

Plant 1					Plant 2					Plant 3							
SEG	N	GM, ppb	GSD	Overall Range, ppb	No. HPET > STEL	SEG	N	GM, ppb	GSD	Overall Range, ppb	No. HPET > STEL	SEG	N	GM, ppb	GSD	Overall Range, ppb	No. HPET > STEL
Engineer support	0	—	—	—	—	Instrument tech	0	—	—	—	—	Laboratory	121	2.57	1.86	0.63 - 347	5
Shift supervisor	0	—	—	—	—	Engineer support	1	0.06	—	0.06	0	Control Rm Op	0	—	—	—	—
						Control Rm Op	0	—	—	—	—	Shift supervisor	4	1.12	2.28	0.54 - 3.48	0
						Process chemist	0	—	—	—	—						
						Technician	4	0.47	1.61	0.24 - 0.67	0						
						Laboratory	0	—	—	—	—						
						Maintenance	20	0.28	2.46	0.03 - 0.68	0						
						Field operator	39	0.3	2.27	0.03 - 0.92	0						
Instrument tech	7	0.29	5.37	0.03 - 2.45	0							Instrument tech	0	—	—	—	—
Laboratory	12	0.57	1.78	0.23 - 1.79	0												
Field operator	47	0.31	5.98	0.03 - 56.2	24	Loading	18	0.52	5.37	0.02 - 18.8	0	Maintenance	16	0.27	5.50	0.03 - 4.26	—
												Field operator	201	4.20	8.33	0.05 - 1726	193
Loading	19	1.89	11.4	0.03 - 200	730	Drumming	4	1.87	4.64	0.43 - 11.3	0	Loading	242	2.86	4.67	0.2 - 189	84
												Drumming	0	—	—	—	—

GM, geometric mean; GSD, geometric standard deviation; HPETs, high potential exposure tasks; ppb, parts per billion; SEG, similar exposure groups.

TABLE 5. Number of Workers Reporting Respirator Use During TWAs and HPETs by Plant/SEG

Plant	SEG	TWAs						HPETs					
		Missing	None	Half	Full	SA	Total	Missing	None	Half	Full	SA	Total
1	Engineer support	8	82	0	0	0	90						
	Field operator	3	80	0	0	37	120	1	7	0	0	39	47
	Instrument tech	8	74	0	1	12	95	1	0	0	1	5	7
	Laboratory	6	95	0	0	0	101	1	11	0	0	0	12
	Loading	8	24	1	0	83	116	0	0	0	0	19	19
2	Shift supervisor	1	97	0	0	2	100						0
	Control Rm Op	0	35	0	0	1	36						0
	Process chemist	0	10	0	0	0	10						0
	Drumming	0	0	4	3	9	16	0	0	0	0	4	4
	Engineer support	0	35	0	0	0	35	0	1	0	0	0	1
	Field operator	2	2	0	0	40	44	1	3	4	0	31	39
	Instrument tech	2	23	0	0	13	38						0
	Laboratory	0	10	0	0	0	10						0
	Loading	1	0	0	0	48	49	0	0	0	0	18	18
	Maintenance	2	14	0	0	27	43	0	0	0	0	20	20
3	Technician	1	34	0	0	5	40	0	4	0	0	0	4
	Control Rm Op	1	94	0	0	0	95						0
	Drumming	0	22	0	0	5	27						0
	Field operator	0	42	0	0	67	109	1	49	0	0	151	201
	Instrument tech	0	76	0	0	3	79						0
	Laboratory	2	101	0	0	0	103	3	118	0	0	0	121
	Loading	0	17	0	0	81	98	0	14	0	0	228	242
	Maintenance	0	32	0	0	18	50	0	11	0	0	5	16
	Shift supervisor	0	86	0	0	4	90	0	3	0	0	1	4
	Total	45	1085	5	4	455	1594	8	221	4	1	521	755

HPETs, high potential exposure tasks; SA, supplied air respirator; SEG, similar exposure groups; TWA, time-weighted average.

high exposures: the number of HPETs and the estimate of the 95th percentile of the TWA exposures.

The method chosen to construct the SuperSEGs has several advantages. For instance, it is not necessary for the sample distribution to follow a normal distribution or have a symmetric distribution. In addition, cut-points for the exposures categories can be chosen to represent meaningful differences in exposure. Also, because the purpose of the clustering procedure was to calculate individuals' cumulative exposures, the choice for determining the SuperSEGs did not depend solely on statistical significance. The between-cluster sum of squares was chosen to provide a small number of SuperSEGs among the Plant/SEGs that clearly clustered together. Although the geometric means for any two SuperSEGs might not be statistically different, the cumulative exposures for workers in one or the other SuperSEG could be substantially different when the geometric means are multiplied by their years of exposures.

Developing SuperSEGs for HPETs was investigated. However, many more HPET samples were collected in one of the plants than in the two other plants, and most of the samples were collected in the last 3 years of the study. Very few HPET samples were collected at the other two plants, and numerous Plant/SEGs in these plants had no, or very few, HPET samples. Because of these substantial limitations in HPET exposure assessment, HPET-based SuperSEGs were not developed.

The estimate of the number of HPET events that exceeded the STEL was calculated and used as an indicator of a worker's exposure to short-term high exposures. This method is less precise at estimating exposures and has inherent uncertainties. The protocol did not specify the method for estimating the number of HPETs conducted, and the method used to provide the estimated number of HPETs performed might have varied from year to year for each HPET within a plant, and it is likely that the method varied between

plants as well. The alternative for assessing short-term high exposures, the estimate of the 95th percentile of the TWA exposures, has been used successfully elsewhere.²³

Although the plants had established policies to use supplied air respirators (airline or self-contained breathing apparatus) during HPETs, numerous HPETs were conducted using no respiratory protection. This might represent a difference between what the plants considered HPETs and what was identified during the discussions with the plants. For example, the plants may have used different engineering controls or work practices that led to a difference in how each plant categorized activities as HPET. Four Plant/SEGs (Plant 1 Laboratory, Plant 2 Engineering Support, Plant 2 Technician, and Plant 3 Laboratory) reported not wearing respirators for any of the HPETs that were sampled.

Also, two Plant/SEGs reported using half-mask air purifying respirators or full-face air purifying respirators while conducting HPETs. It is possible that the data were entered incorrectly and workers actually wore half-mask or full-face supplied air respirators. If they were inaccurately reported, the respirator-adjusted exposures in these two Plant/SEGs could be lower than reported. For Plant 1 Instrument Tech, this would represent about 15% of the samples (1/7), and for the Plant 2 Field operators, this would represent about 10% of the samples (4/39). The respirator-adjusted exposure provides exposures adjusted to an equal or lower concentration based on the APF of the respiratory protection worn. The uncertainty in exposure estimates is compounded when adjusted by a respirator APF.

It is known that the actual concentration inside the respirator can vary greatly both within and between persons.^{30,31} Respiratory protection was determined from the IH sampling form. However, it was uncertain whether respiratory protection was only worn for that task or the entire shift and by a participant in the study. Given that the exposure was adjusted for the entire shift based on the APF and it

is unknown whether the respirator was worn for some or all of the sampled time, the respirator-adjusted estimates contain considerable uncertainty and the actual exposure would likely be higher than the respirator-adjusted exposure used.

Exposure characterization could be improved by collecting samples more randomly, equally including all shifts, and uniformly collecting HPET samples in all plants throughout the study period. Almost all of the samples were collected during routine operations, whereas we set out to also characterize multiple conditions, including upset conditions, shutdown, startup, and turnaround operations. We knew it would be difficult to collect HPETs because they occur intermittently and their occurrence could not be planned in advance. However, more samples were expected given that the sampling period lasted almost 7 years, and samples collected under these various conditions would have provided a more robust understanding of exposures. In addition, they might have changed the Plant/SEGs that were included in the SuperSEGs.

Although many workers in various Plant/SEGs self-reported on the questionnaires that they could smell TDI, the significance of this result is uncertain. It suggests that exposures greater than the STEL may have occurred more often than is indicated by the HPET sample results, and this along with the relationship between self-reporting of smelling TDI and symptoms of asthma need further investigation.

CONCLUSION

The TDI exposure assessment of the primary producers of TDI in the U.S. was one of the most complete to date with over 2300 TWA and HPET samples collected during an almost 7-year period. In a prospective epidemiological study, adequate characterization of exposures is essential to identifying associations with health outcomes. The TDI exposure assessment provided extensive evaluation of TWA exposures during routine plant operations. A sufficient number of workplace TWA exposures to TDI were collected across the Plant/SEGs to adequately characterize quantitative exposures in the Plant/SEGs, and the TWA exposures were used in a novel method to develop cross-facility similar exposure groups. Estimates of cumulative TWA exposures for individuals can be calculated using these data. Respirator-adjusted TWA exposures were calculated, but these exposure estimates contain considerable variability and uncertainty; modifications to the statistical methods would be necessary to support exposure–response analyses, but the specific modifications needed are not clear. A sufficient number of HPET exposures were not collected for a large number of HPETs, so they were not adequately characterized. Therefore, an alternative method to qualitatively represent HPET exposures, the estimated number of HPET events that exceeded the STEL, was calculated to represent the short-term exposures. The arithmetic mean TWA exposure was 0.65 ppb, and the TWA exposures ranged from an estimated 0.01 to a measured 92 ppb. The unadjusted TWA measures and the estimated number of HPET events that exceeded the STEL can be used to support exposure–response analyses.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the many persons who contributed to the success of this study: Persons at the plants who oversaw sample collection and/or collected samples included L. Tanner Martinez and Paulette Rosamond at BASF, John Cikalo and David Coker at Dow Chemical, and Raffie Sessa, Rita D'Angelo, Tim Swords, Bob King, and Amanda Provost at Covestro LLC. Sue Englehart, previously of NIOSH, processed samples and Bob Streicher and Kathy Ernst of NIOSH participated in the evaluation of potential exposure assessment methods and the decision to use the sampling and analytical method used in this study. Kathy Ernst also monitored quality control performance during the study and provided quality control samples. Raj Dharmarajan, Tom Frampton,

Karen Mattson of Covestro LLC analyzed the samples. M. Abbas Virji of NIOSH and Carrie Redlich of Yale University provided many substantive comments that were used to improve the paper.

The authors would also like to acknowledge the original study team, including Edward L. Petsonk, Sue Englehart, Mei Lin Wang, Paul Middendorf, Brent Doney from NIOSH; Pat Conner, William Robert, Gerald Ott, L. Tanner Martinez from BASF Geismar; Jim Chapman, Don Molenaar, Raffie Sessa, Raj Dharmarajan, Barbara Cummings from Covestro LLC; Jean Kasakevich, James J. Collins, John Cikalo, Jaime Salazar (deceased) from Dow Freeport; Liz McDaniel and Athena Jolly from Huntsman; Emmett Russell from the International Union of Operating Engineers; and Sahar Osman-Sypher from the ACC.

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