Acute and Chronic Respiratory Effects of Sodium Borate Particulate Exposures

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This study examined work-related chronic abnormality in pulmonary function and work-related acute irritant symptoms associated with exposure to borate dust in mining and processing operations. Chronic effects were examined by pulmonary function at the beginning and end of a 7-year interval. Time-specific estimates of sodium borate particulate exposures were used to estimate cumulative exposure during the study interval. Change in pulmonary function over the 7 years was found unrelated to the estimate of cumulative exposure during that interval. Exposure–response associations also were examined with respect to short-term peak exposures and incidence of five symptoms of acute respiratory irritation. Hourly measures of health outcome and continuous measures of particulate exposure were made on each subject throughout the day. Whenever a subject reported one of the irritant symptoms, a symptom intensity score was also recorded along with the approximate time of onset. The findings indicated that exposure–response relationships were present for each of the specific symptoms at several symptom intensity levels. The associations were present when exposure was estimated by both day-long and short-term (15-min) time-weighted average exposures. Associations persisted after taking account of smoking, age, and the presence of a common cold. No significant difference in response rate was found between workers exposed to different types of sodium borate dusts. — Environ Health Perspect 102(Suppl 7):119–128 (1994)

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Introduction

In the early 1980s, the California Occupational Safety and Health Administration (CalOSHA) adopted the American Conference of Governmental Industrial Hygienists' (ACGIH) list of threshold limit values (TLVs), thereby converting these from guidelines into legal standards applicable in California. Included on the list were the commercially important forms of sodium tetraborate ($Na_2B_4O_7$), the anhydrous salt, and the pentahydrate and decahydrate containing 5 and 10 moles of water of hydration, respectively. The 10-mole salt is most widely encountered in industry and in the home, and is generally known as borax.

Prior to the legislation, the borate TLVs had been established rather recently by the ACGIH, and were based upon predicted irritant effects of boron dust present in workplace air. In the judgment of the ACGIH, the anhydrous and 5-mole compounds were most irritating. As a result, a TLV of 1 mg/m^3 was established for these, while the TLV for exposures to the 10-mole compound was set at 5 mg/m^3.

Prior to the adoption of the TLVs, exposures to all forms of borates in California were controlled by the same total-dust permissible-exposure-limit (PEL) that OSHA uses elsewhere (10 mg/m^3). Since the newly adopted CalOSHA PELs did not appear to be consistent with the experience of U.S. Borax in their production of these compounds, the company decided to conduct the study reported here.

Today, sodium borates are used primarily in the manufacture of specialized glass, enamels, and glazes; as soldering and welding fluxes; as fat solvents; as fixatives for mordants on textiles; in silk spinning; and in the soap, leather, and cosmetic industries. There are an estimated 420,000 U.S. workers with potential occupational exposure to sodium borates (*1*).

Prior to the study reported here, there had been an earlier study that suggested borate exposure was associated with symptoms of acute respiratory irritation, such as dryness of the mouth, nose, or throat; dry cough; nose bleeds; sore throat; productive cough; shortness of breath; and chest tightness (*2*). Excessive symptoms were reported at levels estimated between 4 and 14.6 mg/m^3. Symptoms were infrequent at exposures of 1.1 mg/m^3. The cross-sectional design of that earlier study had available only sparse information on actual exposure, and had to rely on subjects' recollections of past irritation. The earlier study also reported a reduction of forced expiratory volume in 1 sec (FEV_1) among smokers who had heavy cumulative sodium borate exposure (≥80 mg/m^3-years), but not among less-exposed smokers or among nonsmokers.

The present study was designed with the objective of refining measures of both acute irritation and current exposure in an effort to characterize better the acute exposure–response relationships for sodium borate particulates. In addition, a longitudinal analysis of pulmonary function related to chronic exposure was performed. The study was carried out among U.S. Borax employees exposed to the various forms of borate ore and processed materials present at the Mojave Desert plant site. At this plant, sodium borate minerals, such as tincal and kernite, are mined from an open pit. The resulting ores are processed into refined borate products and packed for shipment in bags or railcars. Three major forms of finished sodium borates are handled in this environment: disodium tetraborate decahydrate—$Na_2B_4O_7 + 10H_2O$, (10 mole); disodium tetraborate pentahydrate—

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$Na_2B_4O_7 + 5H_2O$ (5 mole); and disodium tetraborate—$Na_2B_4O_7$, (anhydrous).

The Irritant Response

Many of the irritant symptoms of sodium borate exposure (sensory irritation of the nose and throat, cough, phlegm production, and bronchoconstriction, as evidenced by a decrease in FEV_1) are part of the respiratory defense reflex, which functions to protect the body from inhaled irritants (*3*). This reflex can be triggered by agents that stimulate receptors in the respiratory tract (*4*). However, little is known about the mechanism by which the irritant receptors are stimulated.

There is evidence that stimulation of the irritant reflex response can occur both as a direct and an indirect response to changes in the osmolarity of the lung-lining fluid (*5–17*) and may be mediated through histamine (*18,19*). Thus, if hyperosmolarity triggers defensive reflex responses, the irritant symptoms reported by sodium borate-exposed workers may be either a direct function of osmolarity or an indirect function of histamine.

Methods

Study Design for Chronic Effects of Exposure

Population and Pulmonary Function Measures. A prospective (follow-up) cohort design was used to examine the associations between change in respiratory health status during the period 1981 to 1988 and exposure during that same period. This design relied on the availability of the 1981 survey results (*2*). The spirometry instrument used in 1988 was the Eagle IIS spirometry system (Warren E. Collins), while that used in 1981 was an Ohio 840 rolling seal spirometer. Both meet the American Thoracic Society/Division of Lung Disease performance criteria and were found in side-by-side evaluations to provide the same results within acceptable spirometer error. Spirometry results were standardized using the prediction equations of Knudson et al. (*20*). A minimum of five (maximum of seven) technically acceptable forced expiratory maneuvers were obtained in 1988, and a minimum of three (maximum of five) were similarly obtained in 1981. In both surveys, repeatability was assessed from the two largest values for each parameter. Subjects were tested without regard to the time of day or day of the work week.

Historical Exposures. Estimates of levels of dust exposure and the definition of separate, homogeneous exposure categories over time were based on examination of current exposure measurements, historical records of exposure, and information on dates of changes in the introduction of exposure controls. Since very little exposure information existed for the years prior to 1978, only interim exposures covering the years between the two surveys were estimated. This information was then organized in a matrix that permitted computation of estimates of interim exposure for each subject.

Estimates of cumulative, interim dust exposure during the 7-year period between the two surveys were computed as a sum of the exposure in each job held in the period, weighted by the number of years between 1981 and 1988 during which the subject worked in that job.

Study Design for Acute Effects of Exposure

In studying the association between sodium borates and acute respiratory irritation, a primary objective was to describe in detail the exposure–response relationships observed when both exposure and response were measured frequently throughout the course of daily work activities. A related question was whether the relationships discovered differed according to the type of sodium borate exposure. As can be seen, the borate types varied only by the moles of waters of hydration in the three chemical forms.

Population and Health Effects. All employees were eligible for the acute study if their exposures to dust could be adequately characterized with respect to borate type. Subjects eligible for the comparison group were identified as current nonoffice, hourly employees who had no routine exposure to borate particulate (other than background). A total of 115 exposed and comparison workers were eligible. All eligibles were invited to participate, and 106 accepted.

At the pre-shift survey, subjects were queried about the presence of a common cold on that survey day or within the past two weeks, about the presence of allergic symptoms or asthma on the survey day, and the time of day they last smoked a cigarette (see Appendix).

To provide close supervision of the study protocol, a technician was assigned to each study subject (2 to 4 subjects were studied per day) and was instructed to stay with that subject throughout the day. The technician was responsible for monitoring the use of the continuous-exposure monitor, and for administering the hourly symptom surveys.

Acute irritant effects were studied in detail through administration of symptom questionnaires before work, and at hourly intervals throughout each of 4 consecutive workdays (see appendix). The closed-ended questionnaires were pilot tested on a separate group of workers who did not participate in the full-scale irritant study. Questionnaires were revised as needed to confirm that symptom queries were understandable. The questionnaire inquired about symptoms of eye, nose, and throat irritation; sneezing; nose bleeds; coughing; and breathlessness. Whenever a subject reported one of these symptoms, the interviewer requested an intensity score and approximate time of onset to the nearest quarter hour. The outcomes were measures of acute irritant symptoms of the respiratory tract and mucous membranes.

Symptom intensity was scored using a category-ratio scale based on Borg's studies of pain or exertion (*21–24*). A score on a scale between 0 and 10 was requested (Figure 1). Subjects were asked to indicate the time of onset to the nearest 15 min within the previous hour (or to indicate when the symptom had persisted from the previous survey). When the analyses were restricted to symptoms of a minimum severity, reports of less severe symptoms were ignored (i.e., considered nonsymptoms).

Only incident symptoms that arose during the workshift were included in the exposure–response analysis. A symptom reported at an hourly survey was defined as an incident symptom if the same type of symptom was not reported in the preceding hour, or the same type of symptom had been reported in the preceding interval but

Numerical value	Severity
0	Not at all
0.5	Very, very little (just noticeable)
1	Very little
2	Fairly little
3	Moderate
4	Pretty much
5	A lot (strong)
6	
7	Very much
8	
9	
10	Very, very much (almost maximal)
•	Maximal

Figure 1. The category ratio severity scale presented to each study participant at preshift and hourly surveys. When an irritant symptom was reported, the participant selected a numerical score to characterize the severity of the symptom.

it could be determined that the symptom had not persisted from one interval to the next. If no second onset time was reported, the symptom was regarded as persistent rather than incident.

In addition to the hourly survey, subjects were provided a means of adding a mark to the exposure monitor each time they experienced an acute irritant symptom (see "Measurements of Acute Exposures"). This device permitted each subject to record the actual time of symptom onset without technician prompting. However, at the hourly survey, the technician would ask whether the marker had been used, and if so, for what symptom.

Measurements of Acute Exposures. A personal direct-reading aerosol monitor (the MINIRAM, Miniature Real-time Aerosol Monitor; MIE Inc., formerly GCA, Bedford, MA) was used in conjunction with a datalogger system, (the Ranger-Rustrak; E. Greenwich, RI). This system provided for the recording of short-interval, real-time exposures.

The MINIRAM aerosol monitor is most sensitive to aerosols in the respirable size range, and like all photometers, is sensitive to high humidity and changes in the particle-size distribution and composition. Since irritation of the eyes, nose, and throat may be caused by particles in the nonrespirable size range, the MINIRAM's use in the study had to be calibrated separately for the three dust types, as well as for different particle sizes.

Throughout the study, the MINIRAM was used in the active mode as a total-dust monitor, with a flow adapter that enabled pumps calibrated at 2 l/min to pull the aerosol through the MINIRAM chamber and onto a closed-faced filter that was subsequently gravimetrically analyzed. To account for the fact that both borates and nonspecific dust may have irritant properties, it was hypothesized that the boron content of dust samples might better represent exposure to borates. Consequently, each filter was also analyzed for total boron content.

A Marple Personal Cascade Impactor with four stages (Anderson Samplers; Atlanta, GA) was used to determine particle-size distributions with cut points for the impactor stages at 21.3, 14.8, 9.8, and 3.5 microns (*25*). A Cahn model 29 electrobalance was used to weigh the filters for gravimetric determinations. All filters were desiccated for 18 hr prior to weighing.

Continuous MINIRAM readings were recorded on a datalogger data tape outfitted with an event-marker button, so that each subject could mark the time(s) an irritant symptom occurred. With this sampling method. it was possible to estimate real-time, total particulate exposure for each subject during each survey day. The instrument, however, cannot distinguish the type of particulate measured. Therefore, sodium borate type was assigned to each daily exposure record based on the type of borate being processed in the area surrounding the individual's work station.

Table 1. Pulmonary function characteristics of follow-up cohort (n = 303).

Category	Mean	SD	Range
FEV_1 (1981) [a]	3.95	0.78	1.49–6.02
FEV_1 (1988)	3.75	0.75	1.23–5.91
% Predicted FEV_1 (1988)	96%	14%	46–137%
FVC (1981)	5.14	0.96	2.23–7.91
FVC (1988)	4.95	0.91	2.12–7.92
% Predicted FVC (1988)	104%	13%	67–148%
FEV_1 Decline + [b]	0.20	0.31	−2.02–1.84
FVC Decline +	0.20	0.38	−2.30–2.39

Abbreviations: FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity. [a] Pulmonary function values reported in liters. [b] + decline = test value in 1981–test value in 1988.

Data Analysis for Acute Effects. The exposure–response analysis of symptoms included detailed examination of exposure as measured by the MINIRAM-integrated estimates of daily (6-hr) and short-term (15-min) exposures. Incidence rates for each symptom were computed as the ratio of the number of episodes to the number of person-hours for which the individual was at risk. Risk ratios, defined as the ratio of the probability in the exposed to the probability in the comparison group, were estimated for each symptom. Categories of increasing exposure levels were then defined, and the incidence was estimated within each category.

To adjust for confounding due to smoking, age, and recent cold, the associations were then estimated in a series of logistic regression models. A separate model was fitted to the data for each of the five most common symptom outcomes.

The exposure–response analyses were based first on daily exposures and then on exposure measured in 15-min intervals. The unit of analysis for the daily exposures was the person-day; and the presence or absence of a particular symptom over the course of the day was paired with the daily, measured exposure. Thus, each person contributed four observations to these analyses, one for each person-day of observation.

In the final phase of the symptom analysis, contiguous 15-min intervals were defined from the start to the end of each observation day. The presence or absence of a symptom was then determined for each interval and paired with the 15-min exposure for that interval. Probabilities of response were estimated across categories of increasing levels. In these stratified analyses, subjects were included up to 96 times, one for each of the 15-min exposure intervals during which they were at risk over their 4 days of monitoring.

These analyses did not satisfy the assumption of independent observations, because multiple observations were made for each subject. Therefore, methods recently developed to account for correlated outcomes in the analysis of repeated measures were also used. Logistic models were fit to the data for each individual with at least three positive symptom reports in the first stage of a two-stage model. Thus, each exposure–response model was based on up to 96 observations. In stage two, the individual odds ratios were summarized using a maximum likelihood estimate of the mean, within strata defined by smoking, cold status, age, and duration of employment. These results have been presented in more detail elsewhere (*26*).

Results

Chronic Pulmonary Function Effects

Loss to Follow-up. Of the 631 workers who participated in 1981, 371 were available for the pulmonary-function retesting in 1988. Of these, 336 performed pulmonary function tests; 303 of the 336 subjects had acceptable tests for both years. Those who were not resurveyed were, on average, 5 years older than those who did participate in the second survey; they also had smoked longer than the second survey participants. FEV_1 differences between the two groups appeared to be accounted for by the differences in smoking.

Follow-up Population. On average, subjects were 44 (± 9.0) years old and had worked for 19 years; the group included 42% current smokers, 28% ex-smokers, and 30% never-smokers. The average 1988

Table 2. FEV_1 decline by smoking status and years employed.

Smoking status	Years employed 0–10	10–20	>20
Never smoker	$n = 9$	$n = 60$	$n = 23$
FEV_1 decline [a]	0.24 (0.08) [b]	0.21 (0.06)	0.17 (0.05)
% pred FEV_1 (1981)	103 (3) [c]	98 (2)	102 (3)
% pred FEV_1 (1988)	103 (2)	97 (1)	102 (2)
>0–10	$n = 4$	$n = 12$	$n = 4$
FEV_1 decline	0.38 (.14)	0.25 (0.06)	0.24 0(.14)
% pred FEV_1 (1981)	104 (2)	99 (3)	93 (6)
% pred FEV_1 (1988)	100 (4)	97 (2)	91 (8)
>10–20	$n = 12$	$n = 28$	$n = 9$
FEV_1 decline	10 (0.08)	14 (0.05)	0.18 (0.13)
% pred FEV_1 (1981)	92 (3)	104 (2)	93 (4)
% pred FEV_1 (1988)	94 (3)	106 (2)	93 (3)
>20	$n = 8$	$n = 83$	$n = 40$
FEV_1 decline	0.16 (0.06)	0.23 (0.04)	0.20 (0.04)
% pred FEV_1 (1981)	104 (5)	93 (2)	92 (2)
% pred FEV_1 (1988)	105 (4)	91 (2)	91 (2)

Abbreviations: FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.
[a] Decline = FEV_1 (1981) – FEV_1 (1988). [b] numbers in parentheses indicate standard error. [c] Percent predicted based on Knudson (*13*).

Table 3. Dose–response model for FEV_1 and exposure with adjustments.

Variable	β	SE	$p>T$
Intercept	−202	83.7	0.017
Cumulative exposure, 1981–1988	−0.000	0.001	0.999
Years employed to 1981	0.45	1.23	0.717
Pack-years, cigarettes	−0.66	0.149	0.001
Age	−3.61	0.373	0.001
Height	4.25	0.448	0.001

Table 4. Regression equation relating FVC decline to 1981 to 1988 cumulative exposure with adjustments.

Variable	β	SE_β	$p>T$
Intercept	−32.29	58.73	0.5597
FVC , 1981	0.78	0.03	0.0001
Exposure, 1981–88	−0.11	0.24	0.6216
Ever smoked	1.45	4.46	0.7439
Age, 1981	−1.07	0.25	0.0001
Height, cm	0.96	0.39	0.0146
	$R^2 = .83$		

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec.

Table 5. Regression equation relating FEV_1 decline to 1981 to 1988 cumulative exposure with adjustments.

Variable	β	SE_β	$p>T$
Intercept	0.62	43.85	0.9986
FEV_1, 1981	0.79	0.03	0.0001
Exposure, 1981–88	−0.07	0.19	0.7122
Ever smoked	−2.50	3.59	0.4860
Age, 1981	−0.91	0.22	0.0001
Height, cm	0.56	0.28	0.0450
	$R^2 = 0.84$		

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec.

FEV_1 and forced vital capacity (FVC) values were 96 and 104% of predicted values, respectively (Table 1). The average annual loss in both FEV_1 and FVC was close to 30 ml/year, the rate of loss expected on the basis of cross-sectional studies in most standard population studies.

Exposure–Response Associations. FEV_1 decline and percentage of loss predicted were examined via duration of work, controlled for smoking status (Table 2). Although years worked was not associated with pulmonary status among never-smokers, evidence for an exposure-related decrease was seen in FEV_1 percent among those who had smoked the longest. To examine these findings further, FEV_1 was regressed on age, height, pack-years of cigarette smoking, and duration of employment (Table 3). These results suggest that once cigarette smoking is accounted for, the effect of exposure duration is not significant.

Since exposure measures were not available prior to the late 1970s, exposure between 1981 and 1988 was estimated for each subject. The method and results for estimating historical exposures are reported elsewhere (*27*). These estimates were compared with rates of loss in function over the study interval. An autoregressive model was used to examine the exposure–response relationship, adjusting for the 1981 pulmonary function level, age, height, and cigarette smoking status. The models explained 83 and 84% of the variability in the 7-year decline in FVC and FEV_1, respectively (Tables 4, 5). After taking 1981 FEV_1 into account, current cigarette smoking status and interim exposure were not statistically significant factors in predicting FEV_1 decline. Nor was duration of employment prior to 1981 a significant factor.

Acute Irritant Effects

Population. A total of 106 subjects participated in the survey of acute health effects of sodium borate exposure. Among the 106, the comparison group was, on average, 7 years older and included more current smokers and workers with longer employment tenure than the exposed group (Table 6).

Exposure: Calibration Study. As noted above, since the MINIRAM cannot separately monitor the different sodium borate aerosols (10 mole borax, 5 mole borax, and anhydrous borax), the calibration study had to be carried out in areas where each of the types was exclusively processed. Over 450 samples were collected in the three dust-type environments. The

Table 6. Demographic characteristics of 106 borax employees in acute study cohort.

Characteristic [a]	Exposed (79)	Comparison (27)
Age	34.0 (7.8)	40.9 (11.1)
Height	69.5 (2.6)	70.3 (3.1)
Sex (male)	78 98.7%	25 92.6%
Race (white)	75 94.9%	26 96.3%
Current smokers	29 36.7%	14 50.0%
Packyears smoking [b]	9.2 (13.8)	14.0 (20.4)
Duration of employment	8.7 (6.3)	11.9 (7.5)
Physical exertion	10.4 (2.5)	8.5 (2.3)

[a] Values are expressed as mean ± SD, or as number and percent. [b] Results are based on 96 subjects (70 exposed and 26 comparison) whose smoking information was complete from the baseline survey.

samples represented dust concentrations ranging from 0.1 to 205 mg/m^3. The types of sodium borate dust do not vary greatly in refractive index or particle size. Nevertheless, the calibration curves were examined for each of the dust types and combinations of dust types to which workers were exposed, to verify that the calibration did not change across dust types. Details of the calibration study are reported elsewhere (*28*). Gravimetric results predicted from the calibration curves were compared with those actually measured in areas not used to generate the curves and were found not to be significantly different. This suggested that the calibration curves could be generalized to all areas in the study.

Personal Exposure Estimates. The environmental sampling activity was undertaken on 432 sample-days (each person sampled for 1 day contributed 1 sample-day). There were only 13 (3.0%) sample-days without complete daily measures and only 2 sample-days without even partial data (0.5%).

Daily versus Short-Term Exposure. The arithmetic mean of daily exposures in the comparison group was 0.45 mg/m^3 total dust (0.02 mg/m^3 total boron), with virtually 100% of the daily levels below 1.0 mg/m^3 total dust and almost 90% below 0.5 mg/m^3. Less than 10% of the 15-min levels were greater than 1.0 mg/m^3. In contrast, average daily exposure for the exposed group was 5.72 mg/m^3 of total dust (0.44 mg/m^3 total boron), with only 21% of the group showing daily exposures of less than 1.0 mg/m^3 total dust, while the majority of exposures were between 1.0 and 10.0 mg/m^3. A total of 68% of the exposed subject-days included at least one 15-min interval when exposure exceeded 10.0 mg/m^3.

Respiratory Irritation: Preshift Symptoms. Preshift symptoms reported by workers surveyed before entry to the workplace were presumed to be unrelated to work. Four of the five symptoms were reported approximately equally by members of the comparison and exposed groups. Only nasal irritation was notably more prevalent in the comparison group (11 of 27 vs 25 of 76). Approximately one-quarter of both groups reported having a cold on the survey day, and more than one-third reported having had a cold in the previous 2 weeks. Although this frequency of colds appears high, the prevalence was the same in the two exposure groups.

Respiratory Irritation: Incident Symptoms. Previous studies of employees exposed to borate dusts included reports of nosebleeds as an important finding. In this study, although subjects were interviewed regularly about them, no nosebleeds were reported. Therefore, nosebleeds are not referred to in any of the tables describing symptoms. Sneezing is represented only in the collapsed category, any symptom, because it was not reported frequently enough to be evaluated separately.

In contrast to the preshift symptom pattern, the frequency of incident reports was uniformly higher among the borate-exposed. The most striking difference was for nasal irritation, where 23% of the exposed group reported at least three incident symptoms, in contrast to none among the comparison group. When incidence rates were calculated for each symptom, the exposed group was almost nine times as likely to report nasal irritation as the comparison group, and seven times as likely to report breathlessness (Table 7). Among those exposed, nonsmokers had higher rate ratios than smokers for nasal (1.3) and eye (16.8) irritation, and lower rate ratios for throat irritation (0.9), cough (0.5), and breathlessness (0.4).

Because dust was measured continuously over the day, paralleling the collection of health data, short-term 15-min and daily exposure levels could be examined in relation to health outcomes. For these analyses, risk was expressed as a probability of response, equal to the proportion of exposure intervals in which a symptom was reported.

Respiratory Irritation: Exposure–Response for Daily Exposures. When examined by daily exposure (Table 8), the probability of nasal irritation increased from 0.01 on days when the daily exposure was less than 1 mg/m^3, to 0.27 when daily exposures exceeded 15 mg/m^3, almost a 30-fold increase. For all five symptoms, the probability of response increased with increasing levels of exposure. These exposure–response trends were statistically significant ($p<0.05$) for all but eye irritation. When these same relationships were examined using estimates of daily exposures to boron in place of total dust the same findings were observed (data not shown).

To adjust for confounding, we included age, current colds, cigarette smoking, and dust level as independent variables in logistic models. The results for each symptom were modeled with subjects included once for each day of observation (generally four times). The exposure–response relationships remained present for all five irritant symptoms (data not shown) with the magnitude of the adjusted risk estimates very close to the unadjusted risk estimates (*29*).

To assess the importance of dust type as well as dust level, a variable for dust type was added to the model. Due to limitations in the distribution of type-specific data, this variable was defined as anhydrous borax versus other. When this type variable was included, it was found not to be a significant risk factor in any of the models.

Table 7. Acute symptom rate ratios.

	Exposed		Comparison		
Symptom	Event	Rate	Event	Rate	Rate ratio[b]
Nasal irritation	152 (1624) [a]	0.09	6 (562)	0.01	8.8
Eye irritation	31 (1792)	0.02	2 (615)	0.00	5.2
Throat irritation	56 (1689)	0.03	7 (609)	0.01	2.9
Cough	89 (1697)	0.05	18 (594)	0.03	1.7
Breathlessness	20 (1771)	0.01	1 (630)	0.00	7.1

[a] Parentheses contain number of 15 min intervals at risk. [b] for all rate ratios, $p<0.001$ based on binomial distribution (one-sided test).

Table 8. Probability of response by TWA-6 dust levels. [a]

Symptoms	Dust concentration, mg/m³ <1	1–4	5–9	10–14	≥15 [c]	Correlation coefficient
Nasal irritation						
Events	7 (877) [b]	29 (765)	44 (266)	36 (120)	42 (158)	
Probability	0.01	0.04	0.17	0.30	0.27	0.964 [d]
Eye irritation						
Events	1 (958)	4 (858)	7 (275)	11 (126)	10 (190)	
Probability	0.00	0.01	0.03	0.09	0.05	0.894 [d]
Throat irritation						
Events	8 (942)	16 (795)	10 (273)	1 (122)	19 (166)	
Probability	0.01	0.02	0.04	0.08	0.11	0.980 [e]
Cough						
Events	30 (920)	32 (792)	14 (278)	8 (120)	23 (181)	
Probability	0.03	0.04	0.05	0.07	0.13	0.929 [d]
Breathlessness						
Events	1 (983)	3 (822)	3 (280)	3 (132)	11 (184)	
Probability	0.01	0.00	0.01	0.02	0.06	0.983 [e]

[a] Dose–response evaluated by weighted least squares method using the midpoint of the dust range for each group. [b] Parentheses contain person-hours at risk. [c] Median (mean) dust level for this category is 23.8 (34.5) mg/m³. [d] $p<0.05$ based on binomial distribution (one-sided test). [e] $p<0.01$ based on binomial distribution (one-sided test).

Table 9. Probability of symptoms of severity ≥3 by TWA-6 dust levels. [a]

Symptoms	Dust concentration, mg/m³ <1	1–4	5–9	10–14	15	Correlation coefficient
Nasal irritation						
Events	5 (877) [b]	10 (765)	21 (266)	24 (120)	18 (158)	
Probability	0.01	0.01	0.08	0.20	0.11	0.859
Eye irritation						
Events	0 (958)	3 (858)	6 (275)	9 (126)	3 (190)	
Probability	0.00	0.00	0.02	0.07	0.02	0.783
Throat irritation						
Events	0 (942)	6 (795)	7 (273)	4 (122)	6 (166)	
Probability	0.00	0.00	0.02	0.03	0.04	0.940 [c]
Cough						
Events	4 (920)	7 (792)	4 (278)	3 (120)	5 (181)	
Probability	0.00	0.01	0.01	0.03	0.03	0.989 [d]
Breathlessness						
Events	0 (983)	0 (822)	2 (280)	0 (132)	2 (184)	
Probability	0.00	0.00	0.01	0.00	0.01	0.018

[a] Dose response evaluated by weighted least squares method using the midpoint of the dust range for each group. [b] ( ) Parentheses contain person-hours at risk. [c] $p<0.05$ based on binomial distribution (one-sided test). [d] $p<0.01$ based on binomial distribution (one-sided test).

Respiratory Irritation: Exposure–Response for 15-min Exposures. To examine how symptoms relate to changes in short-term exposure levels, each full day was divided into 15-min intervals. Fifteen-minute, time-weighted average and symptom status were determined within each short-term interval. Symptom presence within an interval was defined by the onset of an incident symptom. All other at-risk intervals were associated with the absence of a symptom. For convenience, a summary variable (any symptom) representing the presence of any of the irritant symptoms was used in these analyses. Examined by deciles, the probability of an irritant response in a 15-min interval increased significantly from 0.01 in the lowest exposure category (<0.084 mg/m³) to 0.11 when the exposure exceeded approximately 10 mg/m³. Exposure–response associations having been demonstrated using both daily and 15-min exposure measures, both daily and short-term exposure were included in the same logistic regression model. When this was done, a strong, linear, exposure–response trend remained, while the trend for the daily exposures was relatively flat (*29*).

Respiratory Irritation: Short-term Exposure Models. To address the problem of correlated outcomes when examining 15-min exposures within study subjects, separate logistic models were estimated for individual subjects where possible. The 29 subjects who reported a minimum of three incidents of a symptom during the four survey days were identified. Dose–response models were fit to the data for the 25 of these individuals who had complete exposure data. The exposure–response parameters estimated in these logistic models are estimated-odds ratios, (EOR), interpreted as an individual's odds of reporting a symptom given an increase of 1 mg/m³ in 15-min exposure interval.

Ninety percent of the 25 EORs exceeded 1.0. The maximum-likelihood estimate of the EOR among the subjects with multiple positive responses was 1.02 (95% CI: 1.01–1.04) per unit dust. When these odds ratios were stratified by smoking, dust type, duration of employment, recent cold, or age, none of the effect modifiers significantly changed the estimates.

All of the above relationships, using either daily or 15-min estimates of total dust exposures were also examined using estimates of total boron exposures. In every instance, the results were similar (data not shown).

Respiratory Irritation: Multiple Responders. Finally, there was a question as to whether individuals with multiple-symptom reports were more sensitive or more highly exposed. The group of subjects with multiple-symptom reports were younger, smoked less, and were more likely to have a current cold or allergy. However, the multiple responders had substantially higher average exposures (11.2 vs 3.7 mg/m³).

Respiratory Irritation: Acute Symptom Severity. The evidence presented suggests that frequency of irritant events is increased in a sodium borate-exposed work environment. The possibility that intensity of the symptoms reported also increased over background was also examined. This effort took advantage of the fact that, for each symptom reported, the subject was asked to rate its severity. Subjects responded without difficulty to this query; and, as expected, reports of more severe responses were less frequent.

The severity of symptoms reported by comparison-group subjects before they entered the workplace was examined to suggest background severity levels. The results showed that background irritant symptoms were uncommon, and the severity level was lower than that reported for symptoms that occurred at work. Among all comparison subjects without current colds, the average preshift symptom severi-

Table 10. Probability of nasal irritation in an hour by TWA-6 dust levels for different severity levels.[a]

	Dust concentration, mg/m³					
Symptoms	<1	1–4	5–9	10–14	15[c]	Correlation coefficient
Any severity						
Events	7 (877)[b]	29 (765)	44 (266)	36 (120)	42 (158)	
Probability	0.01	0.04	0.17	0.30	.27	0.964[d]
≥Severity 3						
Events	5 (877)	10 (765)	21 (266)	24 (120)	18 (158)	
Probability	0.01	0.01	0.08	0.20	.11	0.859
≥Severity 4						
Events	2 (877)	3 (765)	3 (266)	4 (120)	7 (158)	
Probability	0.00	0.00	0.01	0.03	.04	0.913
≥Severity 5						
Events	1 (877)	2 (765)	1 (266)	0 (120)	3 (158)	
Probability	0.00	0.00	0.00	0.00	.02	−0.308

[a] Dose response evaluated by weighted least squares method using the midpoint of the dust range for each group. [b] Parentheses contain person-hours at risk. [c] $p<0.05$ based on binomial distribution (one-sided test). [d] $p<0.01$ based on binomial distribution (one-sided test).

ty across all symptoms was 1.9, and the average severity for nasal irritation, the most common symptom, was 2.2. Those with current colds reported slightly lower average severity (2.0) for nasal irritation, but higher severity for throat irritation (2.0 vs 0.9) and cough (2.3 vs 1.4).

When the frequency distribution of the severity of responses during the workshift was described, it was found that, among all symptoms, 91% were ≤3 and 96% were ≤4. Thus, there was a virtual cap on the degree of irritation reported in association with current exposures to sodium borate in this setting.

Approximately one-third of the total study time was spent in the lowest exposure category, <1 mg/m³. Among symptoms reported in this exposure category there were virtually none with severity greater than 2, "very little" (Table 9). At exposures greater than 1 mg/m³, however, exposure–response associations were seen for each specific type of symptom of severity ≥3. The trends were similar to those seen when symptom severity was ignored. When examined in logistic models, it again was found that confounders did not alter the significant exposure–response relationships.

Exposure relationships were further reviewed using a stricter severity criterion. Severity levels of ≥4 and ≥5 were examined for nasal irritation; the only specific symptom that occurred with sufficient frequency for such refinement (Table 10). Using either severity criterion, an increasing risk with increasing exposure was observed. The trend for the ≥4 symptom group was statistically significant.

Discussion

The analysis of the relationship of sodium borate exposures in the workplace to chronic effects on pulmonary function could be examined only by evaluating annual, functional decline in relation to exposure between 1981 and 1988. In this analysis, no association was found between FEV_1 and exposure accumulated between surveys. The expected smoking-related abnormalities were observed. Thus, it appears that the 7-year exposure to dust in the work environment examined is not associated with long-term health effects. An effect associated with exposure cumulated prior to the 1981 survey, although unlikely, has not been ruled out.

Having estimated the likelihood of response at different exposure levels, it is possible to consider targets for exposure control. There are no normative data (incidence or prevalence) on the distribution of acute irritant symptoms to use as a guide. The absence of general population rates makes it necessary to make a judgment about an acceptable frequency of irritant symptoms based only on data from this study.

Were the irritant symptoms considered to serve as sentinels of chronic, irreversible changes, it might be required that all symptoms of 3+ severity be prevented. The analysis of the chronic pulmonary function data, however, suggests that this population is not developing chronic pulmonary function decrement attributable to the current work exposures. Although the analysis does not provide a definitive answer to whether the irritant symptoms can be treated only as short-term reversible events, it is sufficiently convincing to suggest that some frequency of moderate irritation (severity level 3) can be tolerated without undue chronic sequelae.

The focus on moderate irritation should be seen in the context of this study's use of a new symptom severity scale. This scale has been adapted following extensive use of similar scales in the evaluation of musculoskeletal and anginal pain. In the results presented above, the severity scale has been shown to provide reproducible and reliable results. In particular, the reported symptoms occurred with less frequency in the higher severity categories, but the exposure response relationships were consistent regardless of severity level selected as a minimum.

It is important to note, however, that the severity scale has not yet been used in other irritant-exposure environments. Thus, although it has been shown to provide internally consistent data within this study, there is limited information on how to interpret the absolute level of irritation associated with a moderate response to sodium borate. Ideally, this scale would have been applied in the field to study other known irritants such as sulfuric acid mist (in a battery plant) or ammonia (in a chemical manufacturing environment). In the absence of such data, one is forced to make the necessary judgments about the absolute level of severity on the basis of data collected with a different severity scale in an experimental, rather than in a field study. The totality of the evidence suggests that the current levels of sodium borate exposures in this plant are generally associated with no more than moderate irritant responses.

The definition of an acceptable level of risk is a difficult and arbitrary one. The exposure limits necessary for control will depend on the health risk of interest. For sensory irritation, in the absence of a chronic effect, some risk is probably acceptable. In this circumstance, then, the selection of an appropriate goal for limits of exposure to borates is likely to depend in part on considerations of technical feasibility and cost.

Lower exposure limits would be required to achieve longer work-related symptom-free periods. Using the data available, an effort was made to estimate the number of hours or days at different daily exposure levels during which an irritant symptom was not probable. The results suggested that a daily exposure level of 1.0 mg/m³ would permit an exposed worker to experience one incident symptom per week, while a daily level of 10.0 mg/m³ would

make more than one moderate symptom per day improbable. Examination of the analogous results for total boron suggested that the same goal would be accomplished if daily levels were kept below 1.0 mg/m^3 of boron.

Differences in the potency of the three dust types were suggested in some of the analyses. These differences, however, were no longer present when confounding was taken into account. In the absence of a specific analytical method to distinguish dust type in environmental samples from the field, type differences cannot be directly evaluated in field samples.

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APPENDIX

U.S. BORAX HEALTH STUDY QUESTIONNAIRE

ID _____ Date _____ Shift ____ Day of Subject's Work Week 1 2 3 4 5

Name _____ Technician _____

1. Do you have a cold today? No ___ Yes ___
2. Do you have allergic symptoms or asthma today? No ___ Yes ___
3. Have you had a cold in the last two weeks? No ___ Yes ___ If yes, when? ___
4. When did you smoke your last cigarette? _____
5. Do you usually breath through your: Nose _____ or Mouth _____
6. Time_____
7. PK Flow Meter Number _____ Readings _____ _____ _____

	Score	Onset
8. Are your eyes irritated today? (This includes burning painful, tearing or in any other way irritated.)	_____	
How recently did this begin?		_____
9. Is your nose irritated today? (This includes runny, stuffy, dry or in any other way irritated.)	_____	
How recently did this begin?		_____
10. Have you had a sneezing bout today? (A bout is considered to be 3 or more sneezes in a row)	_____	
How recently did this occur?		_____
11. Have you had a recent nosebleed	_____	
How recently did this begin?		_____
12. Is your throat irritated today? (This includes sore, dry, scratchy or in any other way irritated.)	_____	
How recently did this begin?		_____
13. Are you bothered by coughing today?	_____	
Is it dry (D) or with phlegm (P)	D / P	
How recently did this begin?		_____
14. Is your breathing bothering you today?	_____	
Is it due to Chest Tightness (CT), Wheezing (W), Shortness of Breath (SOB), or Other (Other)	CT / W / SOB / Other	
How recently did this begin?		_____

REMIND SUBJECT TO PUSH BUTTON WHEN EXPERIENCING SYMPTOMS AND THAT WE WILL ASK THESE QUESTIONS EVERY HOUR

	1	2	3
ID _____	Time _____	Time _____	Time _____
Date _____	Pk Flow _____	Pk Flow _____	Pk Flow _____
	Pk Flow _____	Pk Flow _____	Pk Flow _____
	Pk Flow _____	Pk Flow _____	Pk Flow _____
	Pk Flow _____	Pk Flow _____	Pk Flow _____

1. Score the level of physical exertion felt by your total body during the last hour of work			_____	_____	_____	
2. How many cigarettes have you smoked in the last hour			_____	_____	_____	
3. When did you smoke your last cigarette?			_____	_____	_____	
SINCE THE LAST INTERVIEW	Score	Onset	Score	Onset	Score	Onset
4. Have your eyes been irritated? (This includes burning, painful, tearing, or in any other way irritated.)	_____		_____		_____	
How recently did this begin?		_____		_____		_____
5. Has your nose been irritated? (This includes runny, stuffy, dry, or in any other way irritated.)	_____		_____		_____	
How recently did this begin?		_____		_____		_____

6.	Have you had a bout of sneezing? (3 or more sneezes in a row)	____		____		____	
	How recently did this begin?		____		____		____
7.	Have you had a nosebleed?	____		____		____	
	How recently did this begin?		____		____		____
8.	Has your throat been irritated? (This includes sore, dry, scratchy or in any other way irritated.)	____		____		____	
	How recently did this begin?		____		____		____
9.	Have you been bothered by coughing?	____		____		____	
	Is it dry or with phlegm?	D / P		D / P		D / P	
	How recently did this begin?		____		____		____
10.	Has your breathing bothered you?	____		____		____	
	Is it due to chest tightness (CT) wheezing (W), or shortness of breath (SOB)	CT / W /S OB Other		CT / W /S OB Other		CT / W /S OB Other	
	How recently did this begin?		____		____		____
11.	Did you press the marker?	No ___	Yes ___	No ___	Yes ___	No ___	Yes ___
	How many times?	____		____		____	
	For what symptom(s)?	____		____		____	

RESET TIMER 55 MINUTES