Lens Opacifications Detected by Slitlamp Biomicroscopy Are Associated With Exposure to Organic Nitrate Explosives

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Context: Unusual cataracts (flecks) have been reported to occur at very low levels of trinitrotoluene exposure, but prevalence estimates vary widely. Cataracts have not been reported among workers in the United States exposed to organic nitrate explosives.

Objectives: To determine the prevalence of unusual cataracts in a population of workers in the United States exposed to organic nitrate explosives, to determine whether associations exist with reported cataract risk factors, and to determine if other eye effects (eg, retinal hemorrhage) are associated with exposure.

Design: Cohort prevalence study.

Setting: A university-based ophthalmologic clinic.

Subjects: Sixty-one workers from an explosives plant comprised the exposed group. The comparison group consisted of 56 workers using chemicals other than organic nitrate explosives.

Outcome Measures: The primary outcome measure was opacifications (flecks) of the crystalline lens, graded clinically on a scale of 0 to 4+. Additional measures included visual acuity, applanation tonometry, and clinical evaluation using standard examination techniques.

Results: Sixty-three percent of the workers had anterior cortical lens opacifications in a pattern of peripheral flecks. Exposed subjects were 18 times more likely to exhibit changes than those not exposed, a statistically significant association (95% confidence interval [CI], 5.0-65.0; \(P = .001\)). A statistically significant association with the duration of exposure was also found.

Conclusions: Asymptomatic, low-grade cataracts (flecks) were identified in 63% of the workers exposed to pentolite. No other eye effects were found to be associated with exposure. Cataracts were not associated with other known risk factors, but were associated with the duration of exposure. Biomicroscopy is widely available and useful for detecting changes in the asymptomatic stages.


Organic nitrate explosives, such as trinitrotoluene (TNT), have been used extensively in demolition, construction, mining, and munitions industries. When combined with pentaerythritol tetranitrate (PETN), TNT forms pentolite, another explosive.

During the early 20th century, many toxic effects were found to occur in workers exposed to TNT. Those exposed to high levels of TNT developed aplastic anemia, hepatitis, and in some cases, death; those exposed to lower levels also experienced a variety of adverse effects. The effects of TNT on the eye included cataracts, retinal hemorrhages, and retrobulbar neuritis.\(^1\)

In 1922, Reis discovered retrobulbar neuritis in 2 patients working with pure TNT. In 1946 a case was reported of a 23-year-old worker who had punctate and flame-shaped retinal hemorrhages with papillitis followed 4 months later by a hemorrhage into the vitreous of the same eye. She had been exposed to TNT, dinitrophenol, and dinitro-o-cresol.\(^2\)

Optic neuritis has been attributed to several similar aromatic nitro compounds.\(^2\)

Cataracts were first reported to occur from exposure by Glezerov in 1953.\(^3\) Soviet workers exposed to TNT over the long term were found to have cataracts, which were described by Glezerov as unique. In some cases, the cataracts occurred after as little as 2 years of exposure. A literature review in 1977 found only uncontrolled case series, except for a study conducted in Egypt at a TNT factory. Among only 8 workers and 20 controls, no cataracts were found.\(^4\)

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SUBJECTS AND METHODS

SUBJECTS

The protocol was approved by the Health Sciences Center Institutional Review Board at the University of Utah, Salt Lake City. All currently employed potentially exposed workers at 1 facility were eligible. Workers had varying levels of exposure to pentolite, TNT, and PETN. Process workers, maintenance personnel, and managers were included. Industrial hygiene sampling indicated that air levels were generally below 0.5 mg/m³. Personal protective equipment (gloves, gowns, hairnets, face shields, and goggles) were required. Respirators were provided, but were optional. Observation at the facility indicated that required equipment was generally worn. However, face shields were not routinely in place. Splashes of material were detected on exposed skin, and were found caked on personal protective equipment.

Facility workers who were not exposed to organic nitrate explosives were underrepresented and thus were not a comparable population. Therefore, a comparison population composed of individuals who worked with chemicals was recruited. These workers were recruited individually from a variety of industries and processes. Each worker was prescreened to ensure employment status and also to ensure that there was no history of exposure to organic nitrate explosives. Several were self-employed. Study populations resided in communities with similar UV exposure. Prior to the examination, workers were informed verbally and in writing of the risks and potential benefits of participation. A questionnaire was administered and an in-depth examination was performed. Questionnaires and medical histories were obtained prior to the examination. The examiner was unaware of the exposure status of the subjects. All examinations were performed by the same examiner (N.M.). All clinical examinations were completed prior to data analysis.

CLINICAL EXAMINATION PROCEDURES

Visual Acuity

Best-corrected visual acuity was measured using the Early Treatment of Diabetic Retinopathy Study chart (Bailey-Lovie chart). Vision was tested with the patient wearing corrective lenses if the patient had a refractive error. Acuity was tested before dilation. If visual acuity was not 20/20 OU, a pinhole occluder was placed over the eye and pinhole vision was noted.

Refractive Error

The subject underwent refraction with a phoropter following neutralization of any lenses. The subject’s best-corrected visual acuity was also noted.

Pupil Reaction

Response to light delivered on an ophthalmoscope was measured at distance and any afferent pupillary defect was noted.

Visual Fields

Visual fields were assessed in each eye individually using the finger counting method.

Extraocular Movement

Extraocular movement was assessed in all 6 cardinal positions of gaze and recorded as normal or abnormal. Abnormalities were described.

Intraocular Pressure

Pressure was measured by applanation tonometry (Goldmann) in each eye. The result was recorded in millimeters of mercury.

Cataracts resulting from exposure to TNT have also been reported in China and Finland. Harkonen et al reported a case series in which 6 of 12 workers had cataracts. Cataracts were found only with maximal mydriasis of the eyes and were described as continuous or annular opacities not interfering with visual acuity. Changes occurred in a bilateral and symmetric fashion. Mäkité et al found that 50% to 90% of workers exposed to TNT developed cataracts that were not usually associated with visual acuity loss. Subclinical changes were detectable after low levels of exposure. Of 21 workers exposed to 0.1 to 0.4 mg/m³ of TNT in air, retroillumination photography revealed changes in 83%. Zhou described 413 workers examined annually from 1977 to 1987. He reported that more than 26,000 Chinese workers had been evaluated in various studies and, on average, 17.9% of workers (range, 7.6%–85.2%) were diagnosed as having cataracts. Cataracts occurred even when air levels were below the Chinese exposure limit (1 mg/m³), which is below the current United States standard at 1.5 mg/m³. Zhou stated that although progression could be halted, cataracts would not regress once exposure ceased. None of those reports addressed other risk factors for cataracts.

During our literature review, we were unable to find reports of eye toxicity among workers in the United States, either from TNT or PETN exposure. Penterythritol tetranitrate is currently approved by the United States Food and Drug Administration for the treatment of angina based on animal testing. Few incidences of toxicity have been reported.

Factors previously associated with cataracts include diabetes, other metabolic disorders, elevation above sea level, ultraviolet (UV) light exposure, corticosteroid use, past eye injury or infection, and exposure to toxins. Cataracts are classified by location: cortical, posterior subcapsular, and nuclear. They may have an annular or ring-shaped appearance, or may consist of radial opacities or vesicular changes. The prevalence of subclinical cataracts in the population is unknown. Studies have detected a prevalence of cataracts of up to 47% in the 50- to 59-year age group. However, younger populations are rarely tested because cataracts tend to be a disorder of older age. The age-specific prevalence of cataracts found in the general Utah population is not known, but clinically seems to be very low.

The literature suggests that organic nitrate exposure causes a unique type of cataract, but we were unable to find studies that used comparison populations or that controlled for confounding factors to determine odds.
Biomicroscopy

A slitlamp biomicroscopy was performed. Evaluations of each area of the lens, the eyelid, conjunctiva, cornea, anterior chamber, and iris were made.

Examination of the Crystalline Lens

Slitlamp biomicroscopy followed pupillary dilation. To ensure that age-related changes were graded equally, lens opacities were graded by the Lens Opacity Classification System (LOCS III). Changes found were compared with published examples of the various grades. Unusual lens changes (flecks) were graded on a scale of 0 to 4 because the LOCS III system was unreliable in estimating the scattered and varying nature of the opacifications. Exact location and description of the changes was noted. All grading was performed at the slitlamp by the same ocular pathologist, using the standard comparison plates. The LOCS III system was chosen because of its wide use in cataract research, and the ocular pathologist was trained in its use.

Ophthalmoscopy

Direct ophthalmoscopic evaluation of the optic nerve, retina, and macula were performed. Ophthalmoscopic changes were noted as either normal or abnormal. Abnormalities were described.

Photographs

Color photographs were obtained using the slitlamp camera. Nuclear opacities were assessed by the slit beam illuminating the lens temporally at a 50E angle (original magnification × 16). Retroillumination photographs highlighted cortical and posterior subcapsular opacities (original magnification × 16). Slitlamp photography was used for documentation, not for grading. Standard photographic techniques were used.

RESULTS

One subject with a history of cataracts was excluded from the data analysis. The final study population was composed of 117 workers: 61 workers (122 eyes) in the exposed group, and 56 workers (112 eyes) in the nonexposed group.

The mean age of workers exposed was 42 years (range, 23-64 years). The comparison population had a mean age of 38 years (range, 19-62 years). More women were in the nonexposed population than in the exposed population (15% vs 23%). Information about ethnic or racial groups was not collected; the general population was predominately white. The numbers of subjects from other ethnic and racial groups (eg, Hispanic, Asian, African American) were included in the study.

No subject had diabetes or used insulin or oral hypoglycemics. None had previously reported cataracts. None had histories of metabolic or genetic conditions predisposing them to cataracts, with the exception of hypercholesterolemia (41% exposed, 27% nonexposed).

Routine medication use was comparable (39% exposed, 38% nonexposed). Ten percent of workers in the exposed group used corticosteroids compared with 2% of the nonexposed population than in the exposed population. To test this, we compared the 2 study groups.

We analyzed mixed cataracts by their component parts. A total of 234 observations (2 observations for each subject [each eye]) were used. Unadjusted cataract prevalence rates and 95% confidence intervals (CIs) were calculated. Results were tested by χ2 with continuity correction. All tests were considered significant at the 5% level and 95% CIs were generated to provide a range of plausible values.

Age-adjusted analysis, logistic regression, and the method of generalized estimating equations (GEE) were performed to control for confounding variables and possible modifying factors (eg, UV light exposure). The GEE method was attempted to adjust for correlation between a subject’s right and left eyes. The analyses used the GEEPLUS program, a generalized approach to logistic regression using a logit link and exchangeable correlation structure. To supplement the GEE method, ordinary logistic regression analysis was used to predict the event of any opacifications in either eye.

The frequency of unusual cataracts in nonexposed populations was not known, but assumed to be rare. Sample sizes needed were estimated using only presence and absence of flecks and/or spokes, a dichotomous endpoint. A priori, we determined that this study had more than 80% power to detect an excess risk of 10% in the exposed group if the cataract frequency was between 0.5% and 5%, using 100 workers in each study group. This assumed a 1-tailed test at the 5% significance level. If the prevalence rate was 10% among the exposed workers, the study had more than 80% power to detect 3-fold increased odds. Although the study was smaller than projected, the ORs were much higher and were easier to detect.

Statistical Analysis

The null hypothesis stated that the prevalence of cataracts (by location and grade) was no different in workers who were exposed than in workers who were not exposed. To test this, we compared the 2 study groups.

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exposed group. The use was limited to short-term, topical preparations. The longest duration of use was 18 months, although use of corticosteroids for less than 1 month was more common. Routine use of dietary supplements (eg, vitamins, herbs) was approximately equivalent.

Workers in the exposed group were more likely to use tobacco (current use: 30% exposed, 25% nonexposed; past use: 55% exposed, 50% nonexposed). Mean length of use was 8.3 years (exposed) and 7.3 years (nonexposed). Workers in the exposed group were less likely to use alcohol (current use: 39% exposed, 50% nonexposed; past use: 67% exposed, 78% nonexposed).

Workers in the exposed group reported more routine use of corrective lenses (57% vs 46% for the nonexposed group). More of the workers in the nonexposed group reported visual symptoms. Eye injury rates were similar. More than 90% of the study populations had never had surgery or a diagnosed eye disease in either eye.

The facility in which the exposed group worked used 3 processes. Most of the workers had worked in the pentolite process. Although workers are rotated through jobs, fewer had worked in the PETN process or the nitration process. Mean duration of working in the pentolite process was 5.7 years (range, 0-17 years). Mean duration of working in the PETN process was 2.4 years (range, 0-20 years); 63% had not worked in the PETN process at all. Mean duration of working in the nitration process was 0.2 years (range, 0-4 years); 87% had not worked in the nitration process at all. Workers in the nonexposed group were not asked about these processes.

All subjects were asked about their exposure to 5 nitrates. Because some workers in the nonexposed group had been exposed to nitrates, analyses were performed against these variables to counteract possible misclassification of exposure status.

On examination, abnormalities were noted in lenses and maculae. No abnormalities of posterior subcapsular or nuclear portions of lenses were noted. The Lens Opacity Classification System III (LOC III) classifications for posterior subcapsular portions of all lenses were 0.1, as were the results for both clarity and color of the nuclear portions of all lenses. No subjects in either group had abnormalities of extraocular motion, irises, anterior chambers, discs, or vessels. Of the workers in the exposed group, 1 had scotoma of the right eye, 1 had a macular abnormality in the right eye, and 1 had a macular abnormality in the left eye. No macular abnormalities were identified among nonexposed workers. No flame-shaped hemorrhages or evidence of neuritis were noted in either group.

Anterior cortical lens flecks were common, with no greater than a 0.5 grade difference between eyes. Most subjects' eyes were equally affected. Previously undiagnosed anterior cortical lens changes typical of age-related cataracts were found in 4 workers in the exposed group. Their mean age was 47.5 years (range, 45-51 years). These lens changes were graded as C-1 to C-2 by the LOCS III system and were not included in the analysis. The remainder of subjects had only flecks and spokes. Of workers in the exposed group, 62.9% had peripheral flecks and 11.3% (7 workers) had spokes, of whom 6 also had flecks. In the nonexposed group, 14.3% of the workers had peripheral flecks and none had spokes. Flecks were found in workers younger than 30 years. The mean age of those with spokes was 40 years (range, 29-48 years). Because spokes had been reported in the literature as being associated with TNT exposure, and because a single individual had only spokes without flecks, analysis was conducted for the presence or absence of either flecks or spokes.

Workers employed less than 1 year had no changes (Figure 1A). Trace changes (Figure 1B) were found in some workers employed less than 2 years. One worker employed less than 3 years had changes graded as 1+ (Figure 1C). Only 3 workers employed longer than 10 years did not have detectable changes. The greatest change noted was a 2+ (Figure 1D). Retroillumination of each grade found is shown in Figure 2.

The distribution of refractive errors was comparable. In the exposed group, mean intraocular pressure by Goldmann applanation was 14.54 mm Hg OD and 14.49 mm Hg OS, ranging from 9 to 20 mm Hg. In the nonexposed group, the mean tension applanation measured 15.57 mm Hg OD and 15.76 mm Hg OS, ranging from 10 to 21 mm Hg. While the difference was statistically significant in the right eye, no clinical significance was apparent.

Workers in the exposed group were 10.4 times as likely to have flecks and/or spokes in either eye than those in the nonexposed group (95% CI, 4.0-30.2; P < .001) by crude ratio. Cataracts were associated with age, but not sex. When controlled for age and sex, the OR increased to 11.4 (95% CI, 4.1-36.2; P < .001). When considered by severity of changes, workers in the exposed group were 13.6 times as likely to have changes graded as 1+ or higher than those in the nonexposed group, controlling for age and sex (95% CI, 1.9-610.4; P = .003).

Subjects exposed to TNT were 18 times more likely to have flecks and/or spokes than those who were not exposed (95% CI, 5.0-65.0; P < .001). Those exposed to PETN were 14.1 times as likely to have eye changes (95% CI, 4.4-45.1; P < .001); those exposed to dinitrophenol were 9.6 times as likely to have changes (95% CI, 1.6-56.1; P < .01); and those exposed to nitric acid were 10.4 times as likely to have changes (95% CI, 2.3-47.6; P = .003). An OR of 3.6 for N-orthocresol was obtained (not statistically significant). Only 3 subjects reported N-orthocresol exposure. Trinitrotoluene was the most common substance exposed to the workers in the exposed group.

The probability of changes was not related to tobacco or alcohol use. Those reporting hypercholesterolemia were 3.3 times as likely to have cataracts as were those without a history (95% CI, 1.5-7.4; P = .003). Statistical significance remained, but the OR decreased when analyzed by logistic regression controlling for age (OR = 1.99; 95% CI, 1.05-1.13; P < .001).

Subjects with flecks and/or spokes were no more likely to report vision problems than were those without changes (OR = 1.00; 95% CI, 0.5-2.1; P > .99). They were slightly more likely to wear corrective lenses when controlling for age (OR = 1.09; 95% CI, 1.04-1.14; P = .003).

A model was constructed using a history of injury in either eye, family history of cataracts, a history of hypercholesterolemia, years of residence, years of tobacco use, years of alcohol use, age, and TNT exposure. When tested...
by SAS statistical software (SAS Institute Inc, Cary, NC) logistic regression, the only factor that remained significant was TNT exposure (OR = 23.195% CI, 5.68-94.6; P = .001).

When tested by the GEE, the number of years working in the pentolite process was statistically significant (OR = 1.29; 95% CI, 1.09-1.53; P = .003) for a lens change greater than 0. The effect of exposure during 5 years was even greater (OR = 3.6; 95% CI, 1.5-8.4). Years worked was also significant, even for 1 year of exposure (OR = 1.18; 95% CI, 1.06-1.31; P = .003). The OR increased to 2.3 for a 5-year difference (95% CI, 1.3-3.9).

For lens changes graded 1 or higher, the number of years working in the pentolite process (OR = 1.24; 95% CI, 1.05-1.46; P = .01) and the PETN process (OR = 1.12; 95% CI, 1.00-1.25; P = .05) were statistically significant. Testing the model of years in the pentolite process, years in the PETN process, and years employed, only the years working in the pentolite process remained significant (OR = 1.27; 95% CI, 1.05-1.53; P = .01). The ORs of both exposure to pentolite and exposure to PETN increased during 5-year periods of employment (2.9 and 1.8, respectively). When tested by GEEPLUS, for the outcome of any lens change greater than 0, only the years employed remained significant, with an OR of 1.10 (95% CI, 1.02-1.18; P = .01).

No factor related to UV exposure was significant, including time spent outdoors, wearing UV-blocking sunglasses, and living out of the geographic region.

COMMENT

We found flecks in 63% of workers potentially exposed. Flecks occurred even though exposure levels were generally below the Occupational Safety and Health Administration’s permissible exposure limits and workers were using personal protective equipment. Odds ratios increased when controlling for potential confounding factors, including age. Flecks were documented in workers employed between 1 and 2 years, and in workers younger than 30 years. The longest exposure was 28 years. No flecks resulted in symptoms or reduced vision. The highest grade found was 2+ on a scale of 4+

Flecks were distributed around the periphery of the anterior cortical region. They were uniformly bilateral and equal in grade. Minimal spokes were found only in exposed workers. These may have been age-related, but also were found in young workers. No workers older than 50 years had spokes. With 1 exception, spokes were accompanied by flecks.

Despite the cataracts, the majority of workers in the exposed group had otherwise normal eye examinations. There were few age-related changes noted. While use of published examples may have led to undergrading compared with the use of color transparencies, the grading system was applied equally. There were no significant differences between the study and the comparison popula-
tions for age-related changes. Although macular abnormalities were found only in the exposed group, no conclusion could be drawn. No evidence of neuritis or intraocular hemorrhage was noted. The distribution of refractive errors was similar.

Flecks were found in 14% of the comparison population, all of whom were exposed to a variety of chemicals. The rate of trace changes in that population was unexpectedly high. However, some misclassification could have occurred. Some of the comparison population reported histories of exposure to TNT and PETN, supporting that possibility. However, the statistical significance remained when analyzed by exposure history. The true rate of trace changes in worker populations who have never been exposed to organic nitrates is likely to be less than 14%.

The probability of having changes was highly associated with exposure to TNT and PETN and also may have been associated with dinitrophenol and nitric acid. Association increased with longer periods of employment. Data in this study did not permit us to distinguish among exposure to pentolite, TNT, and PETN, because most subjects were exposed to a mixture of these. A study using biomicroscopic examination of individuals undergoing long-term treatment with PETN for control of angina could indicate whether cataracts are associated with exposure to PETN.

Eye changes were not associated with tobacco or alcohol use. A history of elevated cholesterol levels and cataracts were associated. Because dietary histories and blood cholesterol levels were not obtained, those confounding factors could not be addressed. The association may have resulted from better access to care by those who were exposed than those who were not exposed, many of whom were self-employed. It may reflect different diets: many of the workers in the nonexposed group had lived elsewhere, while most of the workers in the exposed group were long-time residents of the region. Differences in genetic predisposition between the 2 groups could not be eliminated. However, the most likely explanation is that the exposed workers were required to undergo routine surveillance examinations, including routine cholesterol screening. Many of the nonexposed workers were self-employed, young, and healthy. There is a strong possibility that the difference was due to differences in frequency of cholesterol testing, with the association between elevated blood cholesterol levels and cataracts due to the fact that the workers in the exposed group had both exposure and routine cholesterol screening as part of their employment.

Workers in the exposed group were no more likely than those in the nonexposed group to report vision problems. Except for the lens changes, no other eye abnormalities were noted in excess among the study population. Those who were exposed were slightly more likely to wear glasses or corrective lenses routinely when controlling for age. However, they were required to wear safety
goggles or corrective lenses at work. The use of protective eyewear is unlikely to be related to the much higher difference in the prevalence of low-grade cataracts.

Flecks and/or spokes were not associated with diabetes, corticosteroid use, previous eye injury, family history of cataracts, or UV light exposure. Although a greater percentage of the exposed population used corticosteroids, that use was not clinically significant. There was no association with sex. Although our population included members of several ethnic and racial groups, it did not contain sufficient numbers of these individuals to determine if differences existed. Age and duration of employment were collinear. When controlling for age, the duration of employment was still statistically significant.

The GEE method is a powerful approach to incorporating correlated information from the eyes into the analysis. However, idiosyncrasies of the data sometimes caused this iterative procedure to fail to reach convergence of estimates. The almost perfect correlation of outcomes for the right and left eye sometimes seemed to cause computational problems. In these cases, the analysis was supplemented by standard logistic regression to predict the event of changes in either eye. The symmetry of the findings supports the hypothesis that the exposure of each eye to the substances studied is not independent as would be the case if a direct splash to the eye was the mechanism. Either contact through vapors or circulation through the blood could result in symmetrical exposure to the eyes.

Exposure to organic nitrate compounds was highly associated with peripheral flecks of the crystalline lens. Seven workers in the exposed group had spokes that could have been age-related, but may have also represented an effect of exposure. Cataracts (flecks) were bilateral, symmetrical, and asymptomatic; they did not affect visual acuity. The longer a worker was exposed, the more likely that individual was to exhibit lens changes. Changes were seen in workers exposed for periods between 1 and 2 years, and occurred despite the use of personal protective equipment. Changes could be identified using slitlamp biomicroscopy and wide dilation of the pupil. Slitlamp biomicroscopy should be considered as a method of screening for exposure to organic nitrate compounds.

Accepted for publication May 12, 2000.


This work was supported by the Ensign-Bickford Company, Spanish Fork, Utah.

The authors wish to thank Deborah Harrison, MS, for assistance with developing, organizing, and conducting the study; Lizabeth Malmquist Carter and Marie Cason, LPN, for their assistance in conducting the clinical examinations; and Paula Morris, CRA, Doug Blanchard, and Z. B. Krasov, LPN, for their assistance in photography. We also thank Leticia Archuleta, MD, MPH; Jean Bass Angello, RN, and Ginette Speed, RN, for their assistance with data collection and subject recruitment; and Karen Bradakis for clerical assistance.

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