INDUSTRIAL FLUOROSIS

by

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SUMMARY: In 1242 apparently healthy and actively employed workers of a Canadian aluminum facility, the history of musculoskeletal symptoms, of the incidence of fractures, of neck and back surgery, as well as the x-ray findings were reviewed. A highly significant relationship of exposure to fluoride was established with the frequency of back and neck surgery, fractures, symptoms of musculoskeletal disease and past history of diseases of bones and joints in the absence of the typical findings of skeletal fluorosis.

Monitoring exposed workers for the early manifestations of "musculoskeletal fluorosis" is recommended prior to the development of destructive and degenerative changes of the skeleton.

Introduction

In Danish cryolite workers in 1932, Moller and Gudjonsson (1) found extensive involvement of the musculoskeletal system including radioopacity of the vertebrae along with extensive calcification of ligaments and fibrocartilaginous attachments. The most severe manifestations were always found in the vertebral column and pelvis. Since the appearance of Roholm's (2) classic treatise on fluoride intoxication, other scientific workers have reported additional groups of cases of bone abnormalities, in some instances with crippling effects, in men exposed to fluorides in aluminum smelters. CASAW, the Canadian Association of Smelter and Allied Workers, a labor union which represented the workers in a large aluminum smelter, concerned about the increasing numbers of smelter workers with back and neck problems and the possible excessive exposure to fluorides, undertook support of a health effects study of their members.

The overall objective of the study was to determine, by epidemiologic methods, whether exposure to toxic substances in the smelter had adversely affected the health of the workers. This presentation will limit itself to an examination of our findings on the effects of fluorides on the musculoskeletal system.

Material and Methods

The smelter produced in excess of 800 tons of aluminum per day. It emitted 4 - 5 kilograms of fluoride per ton of aluminum into the am-

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bient air. Production started in 1954. The vertical stud Soderburg process is used.

Eligibility for Inclusion into Study: The cohort was selected from a seniority list of hourly employees at the date of onset of the study. Excluded from the study were those on disability leave and those who had worked at the smelter for three months or less. 1242 workers, 85% of those eligible by these criteria, participated.

Each individual filled out a self-administered questionnaire which provided name, birthdate, ethnic and racial background, previous work record and marital status. An interviewer-administered questionnaire collected information on past medical history, symptoms and cigarette smoking. Questions asked included:

Surgery:

Have you ever had spinal fusion? If so, what year?
Have you ever had low back surgery? If so, what year?
Have you ever had neck surgery? If so, what year?

Those answering yes to one or more of these questions in the years after starting work were categorized as having had back or neck surgery following employment. Workers who had surgery at multiple sites or more than once were counted only once.

Fractures: Those answering yes to having one or more fractures on one or more occasions following start of employment were counted only once.

Musculoskeletal Disease History: To examine the past history of musculoskeletal diseases, workers were asked if they had ever been told by a physician that they had arthritis, gout, back trouble, slipped disc or any other significant musculoskeletal medical problems. Workers were counted once if they answered yes concerning one or more of these five conditions.

Musculoskeletal Symptoms: Workers, questioned regarding symptoms of musculoskeletal problems, which included joint pain, back or neck pain, stiffness in the back, stiffness in joints, and swollen joints, were scored as zero for never, one if the problem occurred one to three times per month, two if more than three times per month but less than daily, and three if it occurred daily or was present all the time. The score, the sum of these responses, varied from zero, that is, none of the five symptoms present at any time, to a score of 15, representing all of the five symptoms occurring daily or present all of the time. A score of zero to seven was categorized as low frequency, whereas a score of eight to fifteen was considered a high frequency.

X-ray: A PA chest x-ray and a AP lumbar spine were done and were read by a certified radiologist who knew only the age and sex of the subject but nothing concerning exposure. For bone x-rays, those categorized as "abnormal" included increased density, whiteness, cortical thickening, hyperostosis, blurring of margins and calcification of ligaments. Those considered possibly abnormal included fractures, evidence of bone surgery, renal calculi, other soft calcifications, "other" nonspecific abnormalities, scoliosis and lipping of vertebral bodies.

Exposure Risk Index: Two factors were used in establishing an exposure risk index for each worker. An estimate of the level of concentration of fluoride for each job category in the smelter was made and characterized as high, moderate or low. These were weighted as 0.25, 1, and 2 respectively and multiplied by the duration of exposure of each worker in each job over his entire employment at the smelter to arrive at an exposure risk index. For purposes of analysis, the frequency distribution of the musculoskeletal exposure risk index was used to categorize the entire cohort into low, medium, and high exposure groups.

Workers were divided into four age groups, 18-30, 31-40, 41-50, and 51 years or older. The group ages 18-30 were used because very few workers were under the age of 20 and these were, therefore included. The same is true of the category 51 years or older, since relatively few workers were aged 60 or more.

Results

History of Musculoskeletal Disease: Table 1 and Figure 1 examine the relationship between a history of musculoskeletal disease and exposure to fluoride and compare the frequency of a history of musculoskeletal diseases commencing after employment in the smelter in workers in the high, medium and low fluoride exposure groups. The Mantel-Haenszel chi-square test was used to examine the relationship between those in the highest compared to medium and to the lowest, and medium compared to the lowest category of exposure. The comparison between those heavily exposed with those with minimal exposure reveals striking differences in past medical history. The differences between high and medium groups and medium and low groups suggest a direct relation between an increase in a past history of musculoskeletal disease and an increase in exposure. This relationship is maintained across all age groups. As shown in Table 1, all differences were significant.

Musculoskeletal Symptoms and Complaints: Comparison of the frequency and number of complaints of musculoskeletal symptoms in the past year was made with the level of risk as a result of fluoride exposure as shown in Table 2 and Figure 2. The results were statistically significant, the differences showing themselves particularly in the older age group with the highest exposure.

Neck and Back Surgery: Table 3 and Figure 3 compare the frequency of back and neck surgery as previously defined and performed since commencing work at the smelter with the level of risk of exposure to fluoride. The results were strikingly positive. A comparison of the high to low risk groups revealed no surgery in the younger age groups. As age increased,

Figure 1
Frequency of history of musculo-skeletal diseases (N=1239)

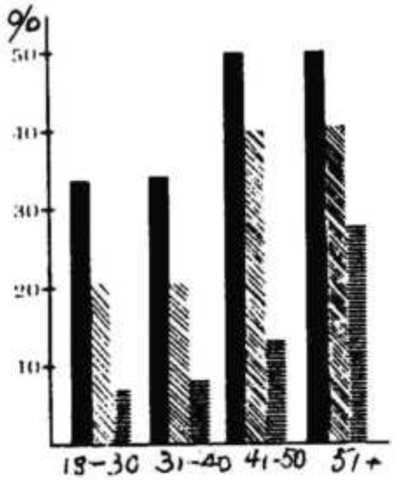

Figure 2
Frequency of symptoms of musculo-skeletal diseases (N=1195)

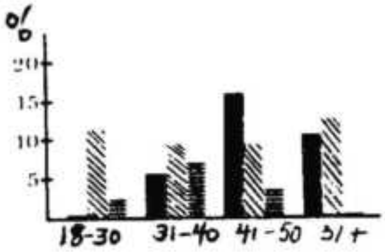

Figure 3
Frequency of back and neck surgery (N=1239)

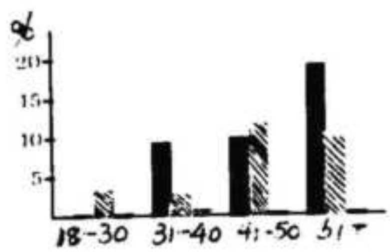

Figure 4
Frequency of one or more fractures (N=1239)

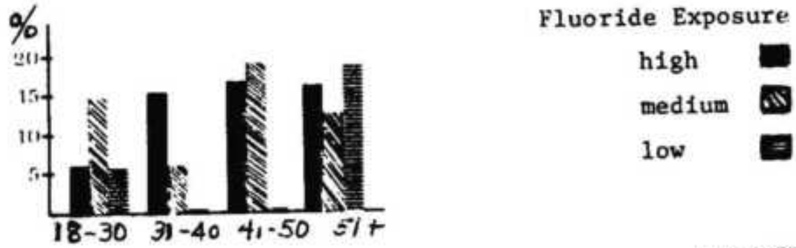

Table 1

Frequency of a History of Musculoskeletal Diseases Commencing after Employment in the Smelter

	Age:	18 - 30	31 - 40	41 - 50	51+	
Exposure Groups	Total Number	Positive History (%)	Positive History(%)	Positive History(%)	Positive History(%)	Mantel-Haenszel χ^2
High	417	33.3% (5/15)	34.6% (27/78)	50% (96/192)	51.5% (68/132)	42.90
Low	407	7.1% (19/268)	8.9% (8/90)	13.2% (5/38)	27.3% (3/11)	$\chi<0.001$
Medium	415	23.0% (46/200)	22.4% (30/134)	40.8% (20/49)	43.8% (14/32)	37.43
Low	407	7.1% (19/268)	8.9% (8/90)	13.2% (5/38)	27.3% (3/11)	$\chi<0.001$
High	417	33.3% (5/15)	34.6% (27/78)	50% (96/192)	51.5% (68/132)	5.00
Medium	415	23.0% (46/200)	22.4% (30/134)	40.8% (20/49)	43.8% (14/32)	$\chi>0.05$ $\chi<0.025$

Table 2

Frequency of Complaints of Musculoskeletal Symptoms

	Age:	18 - 30	31 - 40	41 - 50	51+	
Exposure Groups	Total Number	*High Frequency(%)	High Frequency(%)	High Frequency(%)	High Frequency(%)	Mantel-Haenszel χ^2
High	410	0.0% (0/15)	5.1% (4/78)	15.9% (30/189)	10.2% (13/128)	1.954
Low	381	2.1% (5/243)	6.7% (6/89)	2.6% (1/38)	0.0% (0/11)	$\chi>0.05$
Medium	414	11.6% (23/199)	9.0% (12/134)	10.2% (5/49)	12.5% (4/32)	14.92
Low	381	2.1% (5/243)	6.7% (6/89)	2.6% (1/38)	0.0% (0/11)	$\chi<0.001$
High	410	0.0% (0/15)	5.1% (4/78)	15.9% (30/189)	10.2% (13/128)	0.159
Medium	414	11.6% (23/199)	9.0% (12/134)	10.2% (5/49)	12.5% (4/32)	$\chi<0.10$

* High frequence equals a score of 8-15 points

Table 3

Frequency of Back and Neck Surgery

Exposure Groups	Age: Total Number	18 - 30 % Surgery	31 - 40 % Surgery	41 - 50 % Surgery	51+ % Surgery	Mantel-Haenszel χ^2
High	417	0% (0/15)	9.0% (7/78)	9.9% (19/192)	18.9% (25/132)	10.62
Low	407	0% (0/268)	1.1% (1/90)	0% (0/38)	0% (0/11)	$\chi>.001$ $\chi<.005$
Medium	415	3% (6/200)	2.2% (3/134)	12.2% (6/49)	9.4% (3/32)	11.12
Low	407	0% (0/268)	1.1% (1/90)	0% (0/38)	0% (0/11)	$\chi<0.001$
High	417	0% (0/15)	9.0% (7/78)	9.9% (19/192)	18.9% (25/132)	1.57
Medium	415	3% (6/200)	2.2% (3/134)	12.2% (6/49)	9.4% (3/32	$\chi>0.10$

Table 4

History of One or More Fractures Occurring Since Employment at the Smelter

Exposure Groups	Age: Total Number	18 - 30 % Fractures	31 - 40 % Fractures	41 - 50 % Fractures	51+ % Fractures	Mantel-Haenszel χ^2
High	417	6.7% (1/15)	15.4% (12/78)	17.7% (34/192)	16.7% (22/132)	15.50
Low	407	5.2% (14/268)	0% (0/90)	0% (0/38)	18.2% (2/11)	$\chi<0.001$
Medium	415	14.5% (29/200)	6.0% (8/134)	18.4% (9/49)	12.5% (4/32)	19.52
Low	407	5.2% (14/268)	0% (0/90)	0% (0/38)	18.2% (2/11)	$\chi<0.001$
High	417	6.7% (1/15)	15.4% (12/78)	17.7% (34/192)	16.7% (22/132)	0.99
Medium	415	14.5% (29/200)	6.0% (8/134)	18.4% (9/49)	12.5% (4/32)	$\chi>0.10$

surgical intervention in those at high risk due to exposure increased remarkably to almost 20% in the 51+ categories compared to 0% incidence in the same age group in those who had little or no exposure. A very significant increase in incidence of surgery is also noted when medium and low categories are compared. When the high and medium exposure groups were compared, the results were not statistically significant at the $p<0.5$ level although those in the higher category reported surgery in 19% as compared to approximately 9% in those moderately exposed.

Fractures: Table 4 presents a comparison of the frequency of the history of one or more fractures occurring since employment at the smelter, among those with a high, medium and low fluoride exposure index Table 4 shows that high and low exposure groups, and medium and low exposure groups have a different incidence of fractures at a statistically significant level. A comparison of the high to medium exposure group did not achieve a statistically significant level of association. The biggest differences were seen in the age groups from 31-40 and 41-50.

X-ray Findings: In contrast to the above findings, comparisons of the high to low, medium to low and high to medium groups revealed no significant differences in the frequency of bone x-ray abnormalities when standardized for the four age groups. Whereas many had nonspecific abnormalities, few had evidence of the dense bone described as "fluorosis" by Roholm and others in early studies.

Discussion

As a result of considerable effort by the union and due to workers' concern for their health, 85% of those eligible participated in the study. Of the 216 who failed to appear for testing, questioning, and examination, only 46 were due to outright refusals. The other 170 were on vacation, absent from work or, for other reasons, did not appear for the examination. This was a cross-sectional study, that is, it examined only supposedly healthy and actively employed workers. It was, therefore, in fact a study of a "survival" population. Any abnormal findings represent a most conservative estimate of the problem since those who left employment or were absent because of illness were not examined. Further, internal controls were used because the community is isolated and most of its able-bodied men work in the smelter. Since even the "controls" had some degree of exposure, differences between exposure groups would tend to be minimized so that when medical problems do appear, they can be assumed to be at least as serious as we found them.

The personal exposure risk index based on the entire job history and duration of exposure appeared to be a useful method for quantitating risk among the workers. We have also developed and previously published personal risk index for other organ systems which estimates levels of risk based on duration, intensity, and multiplicity of exposures, and intrinsic toxicity of the chemical agent, which appears useful in more precisely quantitating risk where multiple agents act on the same organ system (3).

The classic cases of fluorosis described by Møller and Gudjonsson (1) and by Roholm (2), and the epidemics of fluorosis found in India are not seen very often today although Kaltreider et al. (4) found that 96% of the 79 potroom workers he examined had varying degrees of skeletal fluorosis. Where fluorosis or exposure to fluorides has been studied, there is considerable evidence that the back and neck are among the first and most severely affected skeletal areas. Moller and Gudjonsson, and Roholm in their studies remarked on the stiffness of the back and complaints by the workers of rheumatic pains. Agate et al. (5) found abnormal x-rays in more than 25% of heavily exposed potroom workers with symptoms of musculoskeletal disease but without the classical signs of fluorosis. Vischer et al. (6) found in 17 heavily exposed potroom workers ossification of spinal ligaments and outgrowths of bony spurs on the vertebrae but in only nine was density of the pelvis and lumbar spine increased on x-ray. All except one complained of pain and stiffness of the extremities, shoulder, neck and lower back.

Similar findings of musculoskeletal changes without classic x-ray signs of fluorosis in workers exposed to high levels of fluorides have appeared in a number of other studies. Of special importance is the large prospective study by Zislin and Girskaya (7). They followed 2738 workers from the time they first came to work in an aluminum smelter and compared them with 1700 others employed in a nonfluoride producing industry. They found that nonspecific bone changes, musculoskeletal symptoms and other findings antedate the classic x-ray changes of fluorosis in the bones by five to seven years and concluded that the changes of fluorosis described by Roholm represent the late stage of the disease.

Our findings demonstrate a highly significant relationship between the frequency of back and neck surgery, fractures, symptoms of musculoskeletal disease and a past history of diseases of the bones and joints. In the absence of so-called classic fluorosis, a disease complex was established which involves much more than merely the radiologic appearance of dense bone. Since more stringent regulations in many countries have resulted in reduced exposure to fluorides, it is reasonable to examine workers and watch for these findings instead of waiting for dense bone to appear which is related to massive exposure to fluoride. This conclusion is supported by our findings of a statistically significant, direct correlation between back and neck surgery and a past history of other bone and joint disease, with a high fluoride exposure risk index. The relationship between those having back and neck surgery following employment and increased fluoride exposure was highly significant when compared within and among age groups based on the Mantel-Haenszel chi-square analysis.

Various theories have been advanced to explain the concentration of fluoride in the lumbar and cervical spines. Two factors should be considered. In the study by Pandit (8) in 1940 of Indian basket weavers exposed to fluoride, it was observed that the much used left arm and wrist were particularly susceptible to fluorotic exostosis. Additionally, Ascenzi (9) found that the pattern of ^{18}F distribution in the skeleton is determined by the supply of blood to a bone with increased deposition in those bones receiving the most blood. If this is true, the areas suffering repeated or constant stress or trauma, and as a result requiring ongoing repair, may be areas of increased circulation and metabolism and, as a consequence, increased deposition of fluorides.

The highly significant correlation between exposure to fluoride and fractures which we found has not, as far as we know, been reported previously in the literature. Because of concern about this possibility, studies were carried out to examine whether this might occur. An early study by McClure (10) in 1944 compared high school teenagers and young armed forces recruits from communities with varying amounts of fluoride in the water. The levels of exposure were considerably less than those in the smelter and the groups were much younger. McClure found no differences in fracture experience. Our findings are important in view of administration of fluorides in fairly high doses in treatment for osteoporosis, particularly in the elderly, for the purpose of increasing bone density and bone strength. In light of our findings, further consideration should be given as to whether such treatment truly increases bone strength as opposed to bone density. The increased density noted on x-ray often appears to be due, not to a true increase in bone mineralization, but rather to exostotic thickening of the bone. We feel that one cannot equate the x-ray findings with the degree of calcification or physical strength of bone. In fact, multiple studies have suggested that frequently the bone in fluoride intoxication is less dense and less mineralized than normal and that there is evidence that high levels of absorption of fluorides are associated with decreased mineralization. Thus, whereas the bone may appear more dense radiologically, it may, in fact, be more fragile and more susceptible to fracture. Our findings of a highly significant increase in fractures in the high fluoride exposure group suggests that this may indeed be the case. Further, in one study, those receiving fluorides as treatment complained of joint pain and tenderness, symptoms similar to those experienced by the workers we examined.

In conclusion it would appear that classic skeletal fluorosis, is in fact a far advanced manifestation of a disease which may present a variety of musculo-skeletal symptoms including abnormal fracturing of bone and of much earlier occurrence pathology of the cervical and lumbar vertebrae. Given the improvements in the work environment and air quality in the past decade, it is more appropriate to monitor exposed workers for the early manifestations of the disease complex which we have described, and which we call musculoskeletal fluorosis, before the degenerative and destructive changes of the vertebrae, joints and other bony structures make their appearance.

Acknowledgement

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FLUORIDE BRIEF

Enflurane (CHF_2OCF_2CHClF) undergoes oxidative dehalogenation in the liver to form difluoromethoxydifluoroacetic acid ($CHF_2OCF_2CO_2H$) together with chloride ion and renally toxic amounts of fluoride ion. When the C-H bond in the -CHClF group of enflurane or in the -CHCL- group of isoflurane ($CHF_2OCHClCF_3$) is replaced with the more resistant C-Cl bond, almost no fluoride ion is released from either anesthetic in rat liver microsomes. These results suggest a way to design safer, less toxic fluorinated anesthetics.

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