17187

20

ARSENIC AND RESPIRATORY CANCER IN MAN: FOLLOW-UP OF AN OCCUPATIONAL STUDY

Anna Lee-Feldstein
Biostatistics Department
The University of Michigan
School of Public Health
Ann Arbor, MI 48109

The earlier report by Lee[1] and Fraumeni on the mortality experience of 8047 white male copper smelter workers exposed to arsenic trioxide in western United States followed the mortality of the group during the period 1938-63. The present study is a follow-up of the same group with mortality observed during 1938-77. The group of men were found to have an excess in total mortality when compared with white males in the same region, due largely to respiratory cancer, diseases of the heart, emphysema, and vascular lesions of the central nervous system. Three hundred and two men in this group had died of respiratory cancer by late 1977, nearly three times the expected number. The excess respiratory cancer mortality increased with length of employment and was positively related to degree of arsenic exposure, with more than five times as many deaths as expected found in the heavy arsenic-exposure group.

1. Introduction

In a study supported by the National Cancer Institute, Lee and Fraumeni [1] reported in 1969 on the mortality experience during 1938-63 of 8047 white male workers exposed to arsenic trioxide in a copper smelter in western United States. A comparison was made with the mortality of white males in States in the same area, and a threefold increase in respiratory cancer deaths was observed among the smelter employees. The excess in respiratory cancer mortality was as high as eight-fold among men working more than 15 years and heavily exposed to arsenic; further, it showed a gradient in proportion to level of arsenic exposure. Findings of the study were in support of the hypothesis that inhaled arsenic is a respiratory carcinogen in man, although the influence of sulfur dioxide and other chemicals present in the smelter could not be discounted.

Since the Lee and Fraumeni paper was published, several studies of copper smelter workers have reported excesses in respiratory cancer [2-7]. The most recent of these, by Lubin et al. [7], surveys the mortality experience of the Lee-Fraumeni study group for the period 1964-77 only and relates this mortality to smelter employment prior to 1964. The present study was designed as a broader follow-up of the Lee-Fraumeni

[1] Present author

study; it includes 1) mortality information from both the Lee-Fraumeni study and the Lubin study, 2) smelter employment experience prior to 1964 (from Lee and Fraumeni) and 3) recently collected smelter employment experience for the period 1964-77. The total period of mortality follow-up for the present study is 40 years (1938-77) and this mortality is related to the complete smelter employment experience of the study group through September 30, 1977.

2. Methods

Included in this study were 8045 white males in the Lee-Fraumeni study. These men were employed at the smelter for 12 or more months prior to December 31, 1956, and their mortality experience was observed from January 1, 1938, to September 30, 1977.

Smelter employment information for the period January 1, 1964, through September 30, 1977, was obtained for this study from company records. Mortality follow-up information was obtained from company records, Social Security Administration records, and death registers of various State health departments. Table 1 summarizes the status of the study group at the cut-off date of the present study. Compared with the Lee-Fraumeni study, nearly twice as many men were deceased by September 30, 1977.

Table 1 Status of study group, September 30, 1977

Known to be living		3679
Employed by smelters	442	
Other[a]	3237	
Known to be deceased		3550
Not known to be living or deceased		816
Total study group		8045[b]

[a]Includes persons receiving benefits or making claims to Bureau of Old Age and Survivors Insurance after September 30, 1977.

[b]Two persons in the original study group of 8047 who were females have been deleted.

Death ce
smelter worke
period, 1964-
fied accordin
Diseases and
revision codi

The life
analyze morta
observation.
end of one ye
prior to that
study when lo
were assigned
on the basis
of employment
of various pe
It should be
than Lee and

Table 2 Des
smelter worke
of smelter em
1977).

Length o employment g	
1 (25 or mo	
2 (15 to 24	
3 (10 to 14	
4 (5 to 9 y	
5 (1 to 4 y	
TOTAL	

[a]Employees in

[b]Group assign
termination
was earlier).

[c]Represents c
1938-77, wit
period 1964-
pleting 1 ye
a full year
period, empl
work experie

Death certificates and vital statistics tapes were obtained for the smelter workers known to have died during the additional observation period, 1964-77. For this period, underlying causes of death were classified according to the seventh revision of the International Lists of Diseases and Causes of Death [8], which is quite comparable to the sixth revision coding used by Lee and Fraumeni for deaths occurring before 1964.

The life table method [9] as programmed by R. Monson [10] was used to analyze mortality of the smelter workers over the entire 40 year period of observation. Individual workers were entered into the life table at the end of one year of employment or in 1938, if employed at least 12 months prior to that date. Persons lost to follow-up were withdrawn from the study when lost. For each calendar period in the analysis, individuals were assigned to one of five groups (called cohorts by Lee and Fraumeni) on the basis of their total years of employment (table 2). These length of employment groups were selected to clarify the effect on mortality of various periods of exposure to environmental agents in the smelter. It should be noted that groups 1 and 2 are defined somewhat differently than Lee and Fraumeni's cohorts 1 and 2.

Table 2 Description of length of employment groups, with number of smelter workers, numbers of deaths, person years at risk, and duration of smelter employment (based on total work experience through Sept. 30, 1977).

Length of employment group[a]	Number of persons[b]	Number of deaths	Number of person years of follow up[c]
1 (25 or more years)	1899	1169	27,053
2 (15 to 24 years)	1138	586	26,556
3 (10 to 14 years)	678	328	19,734
4 (5 to 9 years)	1082	433	30,854
5 (1 to 4 years)	3248	1006	88,279
TOTAL	8045	3522	192,476

[a] Employees in all cohorts were living on Jan. 1, 1938.

[b] Group assignment of each person here was based on his status at the termination of employment or on September 30, 1977 (whichever date was earlier).

[c] Represents cumulative follow-up experience over the study period, 1938-77, with a total of 67,569 person years of follow-up in the period 1964-77. Individuals were initially counted at risk upon completing 1 year of employment or on Jan. 1, 1938, if employed at least a full year before that date. In each calendar year of the study period, employees were counted in the group reflecting their cumulative work experience to date.

The study group was compared with the combined white male population in Idaho, Wyoming and Montana by applying age- and cause-specific death rates for 5-year age groups and for the calendar intervals (1938-42, 1943-47, etc.) for these states to the study population at risk, thus obtaining expected deaths for our study group for each cause. Expected deaths were then summed over age groups and calendar periods to obtain total expected deaths by cause. Observed and expected deaths were compared by the standardized mortality ratio (SMR = (observed/expected)X100).

To determine the effect of arsenic on mortality, the study group was categorized by exposure to various levels of arsenic. From measurements made in the smelter, each work area in the smelter had been rated on a scale from 1 to 10, indicating the relative amount of arsenic trioxide (AS_2O_3) in the atmosphere [11]. Arsenic exposure associated with smelter operation is documented elsewhere [12-14]. As in the Lee and Fraumeni study, jobs in the areas known as the arsenic kitchen, Cottrell, and arsenic roaster were rated as "heavy" arsenic exposure areas. "Medium" arsenic exposure was associated with four work areas known as the converter, reverberatory furnace, ore roaster and acid plant, and casting. All other job areas had "light" arsenic exposure. Measurements in the work areas may have varied over time, but it is reasonable to assume that the 3 broad categories denoting relative exposure to arsenic remained fixed. Since most men worked in several different areas, to be conservative we classified each individual into the one of three arsenic categories denoting his heaviest (maximum) exposure to arsenic during his entire smelter work experience.

3. Results

We observed 3,522 deaths in the entire study group, compared with 2,729 deaths expected ($p < 0.01$). Of the thirteen specific causes of death considered, tuberculosis, digestive and respiratory cancer, vascular lesions of the central nervous system, diseases of the heart, emphysema, and cirrhosis of the liver showed a significant excess of observed over expected (table 3). Similar results were observed in the Lee and Fraumeni study for tuberculosis, respiratory cancer, diseases of the heart and cirrhosis of the liver. When the causes of death shown in table 3 were analyzed further by length of employment group, respiratory cancer was found to be highly significantly in excess of expectation in each group. Further, respiratory cancer SMR's increased monotonically with length of employment, agreeing with findings in the Lee-Fraumeni study (table 4).

Smelter workers in each of the three arsenic-exposure groups had significant excesses in respiratory cancer mortality (table 5). A definite gradient was associated with degree of arsenic exposure, with the ratio of observed to expected mortality from respiratory cancer being approximately 5.1, 4.5 and 2.3 in heavy, medium, and light arsenic-exposure groups, respectively. This result is in accord with earlier results of Lee and Fraumeni (except that their reported excess for men with heavy exposure to arsenic was 7 times expected). With the exception of length of employment group 1, the excess in respiratory cancer mortality increases with increased degree of exposure to arsenic

Table 3 Ob
standarized

Cause of Dea
Tuberculosis
Respirator
Other
Malignant ne
Digestive
Respirator
Other
Vascular lesi
central ne
system
Diseases of h
Influenza and
Emphysema (19
Cirrhosis of
Accidents
Motor vehic
Other
Suicide and h
All other cau
Total

[a] Seventh revis
[b] SMR = (observ
[c] Significant a
[d] Among the 302
bronchus (162
in 3 and (160
[e] Includes 19 e
death rates a

Table 3 Observed and expected deaths due to selected causes, with standarized mortality ratios (SMR's) among smelter workers, 1938-77.

Cause of Death	List No.[a]	Number of deaths Observed	Expected	SMR[b]
Tuberculosis	001-019	53	27.93	190[c]
Respiratory	001-008	47	25.51	184[c]
Other	010-019	6	2.42	248
Malignant neoplasms	140-199	609	370.74	164[c]
Digestive	150-159[d]	167	133.58	125[c]
Respiratory	160-164[d]	302	105.81	285[c]
Other	140-148, 165-170, 177-181, 190-199	140	131.35	107
Vascular lesions of central nervous system	330-334	262	211.56	124[c]
Diseases of heart	400-443	1366	1056.55	129[c]
Influenza and pneumonia	480-483, 490-493	88	76.05	116
Emphysema (1963-77 only)	527	90	34.58	260[c]
Cirrhosis of liver	581	76	36.53	208[c]
Accidents	800-962	288	280.27	103
Motor vehicle	810-825, 830-835	106	115.55	92
Other	800-802, 840-862	182	164.72	110
Suicide and homicide	963-964, 970-979, 980-985	83	86.08	98
All other causes	Residual	606[e]	548.50	
Total		3522	2728.79	129[c]

[a] Seventh revision of International Lists of Diseases & Causes of Death.

[b] SMR = (observed/expected) x 100.

[c] Significant at 1% level. [15]

[d] Among the 302 deaths from respiratory cancer, the site was lung and bronchus (162,163) in 289 cases, larynx (163) in 9, mediastinum (164) in 3 and (160) in 1.

[e] Includes 19 emphysema deaths occuring before 1963, when emphysema death rates are not available for individual states.

Table 4 Observed and expected deaths for respiratory cancer, with standardized mortality ratios (SMR's), by length of employment group, 1938-77.

Length of employment group	Respiratory cancer deaths		
	Observed	Expected	SMR
1 (25+ yrs)	127	31.14	408[a]
2 (15-24 yrs)	44	17.00	259[a]
3 (10-14 yrs)	25	10.77	232[a]
4 (5-9 yrs)	29	12.73	228[a]
5 (1-4 yrs)	77	34.16	225[a]

[a]Significant at 1% level.

Table 5 Observed and expected deaths from respiratory cancer, with standardized mortality ratios (SMR's), by degree of arsenic exposure, 1938-77.

Respiratory cancer mortality	Maximum exposure to arsenic (12 or more months)[a]		
	Heavy	Medium	Light
Observed	33	93	136
Expected	6.45	20.85	58.86
SMR	512[b]	446[b]	231[b]
(Number of men in (arsenic category[a]	451	1585	4448)

[a]The remaining 1562 men in the study worked less than 12 months in their category of maximum arsenic exposure and had an SMR of 204 (40 observed respiratory cancer deaths and 19.64 expected).

[b]Significant at the 1% level.

in the variou
group of men
medium exposu
ratory cancer
"medium" arse
in the earlie

The late
exposure grou
to death. Si
we considered
separately fr
aged 30 and u
39.5, 42, and
arsenic expos
62 years, res
group were on
remainder of
over thirty a
(23 years) fo
observed later
heavy, medium

The exces
was due largel
and vascular
was observed f
spiratory canc
with length of
other causes i
agents in the

The smelt
from respirato
of arsenic exp
agents in the
mortality. Ad
table calculat
cancer rates a
likely that th
mortality asso
explained by f
status, medica

Cigarette
[16]. Smoking
available. Sm
involving a sa
gators in that
smoking alone
seen among smel

in the various length of employment groups. (Group 1 contains a large group of men first employed prior to 1925 and, for this group, men having medium exposure to arsenic had the greatest observed excess in respiratory cancer mortality. It is possible that jobs identified as "medium" arsenic areas involved intermittant heavy exposure to arsenic in the earlier days of the smelter operation.)

The latent period for respiratory cancer in our three arsenic-exposure groups was estimated by the interval from first employment to death. Since age at first employment is an important covariate, we considered men who were over 30 years of age when first employed separately from men aged 30 and under at first employment. Among men aged 30 and under at first employment, the median latent period was 39.5, 42, and 39 years, respectively, for heavy, medium and light arsenic exposure groups, with maximum latent periods of 55, 62, and 62 years, respectively, in these groups. Men in the medium exposure group were on the average 2 years younger at first employment than the remainder of the group first employed at age 30 or under. Among men over thirty at first employment, the median latent period was the same (23 years) for all arsenic-exposure categories; however, the maximum observed latent period was 43, 53, and 55 years, respectively, for heavy, medium and light arsenic exposure groups.

4. Discussion

The excess of observed deaths among smelter workers in this study was due largely to respiratory cancer, diseases of the heart, emphysema, and vascular lesions of the central nervous system. No excess mortality was observed for pneumonia and influenza. Except for mortality from respiratory cancer, no significant cause of death showed a positive gradient with length of employment, which is an indication that mortality for these other causes is related to factors other than exposure to environmental agents in the smelter (including other work experience).

The smelter workers had nearly a threefold excess in observed mortality from respiratory cancer, with a positive gradient associated with degree of arsenic exposure. We also considered factors other than environmental agents in the smelter which might be related to respiratory cancer mortality. Adjustments for differences of age have been made in the life table calculations, thus removing the effect of increasing respiratory cancer rates associated with increase in age. Further, it hardly seems likely that the excess of respiratory cancer deaths and the gradients in mortality associated with exposure to arsenic in the smelter can be totally explained by factors affecting respiratory mortality, such as socioeconomic status, medical care availability, and genetic susceptibility.

Cigarette smoking and lung cancer have been linked in numerous reports [16]. Smoking histories for all persons in the present study were not available. Smoking histories have been collected for an independent study involving a sample of 1800 men from the present study group. The investigators in that study have indicated that their findings suggest that smoking alone does not account for the observed respiratory cancer excess seen among smelter workers in the present study [17].

The excess we are seeing here in respiratory cancer deaths among smelter workers is most likely related to exposure to carcinogenic agents in the workplace. Arsenic has been investigated in many non-mining occupational studies as a potential carcinogen in man, many of them published since the Lee and Fraumeni study [2-7, 18, 19]. The percentage of deaths due to respiratory cancer is quite similar in these studies, except for the large percentages reported among insecticide manufacturers by Ott et al. [18] (21%) and among copper smelter employees in Japan by Tokudome and Kuratsune [2] (18.5%). The collected evidence from the present study and others cited here supports the hypothesis that arsenic is a respiratory tract carcinogen among various occupationally exposed groups.

It is possible that other agents in the smelter which are correlated with levels of arsenic, such as SO_2, may enhance the hypothesized carcinogenic effect of arsenic. But, our findings continue to support the hypothesis of Lee and Fraumeni, stated more than 12 years ago: "...exposure to high levels of As_2O_3, perhaps in interaction with SO_2 or unidentified chemicals in the work environment, is responsible for the excessive number of respiratory cancer deaths among smelter workers."

The author wishes to thank the Environmental Epidemiology Branch of the National Cancer Institute for its support in collection of data used in this study; special recognition is due to Linda M. Pottern and B.J. Stone (NCI) for their diligent efforts in determining vital status of the study group and in the acquisition and coding of death certificates. Also to be thanked are those staff members of the Epidemiology Department of the University of Michigan who were responsible for the careful collection and coding of recent employment histories.

[1] Lee, A. man: a (1969).

[2] Tokudom cancer Cancer,

[3] Rencher western

[4] Pinto, S arsenic

[5] Wall, S. Int. J.

[6] Enterlin Am. J.

[7] Lubin, J Fraumeni recent n

[8] World He Classifi World He

[9] Cutler, method i

[10] Munson, Computer

[11] Hendrick

[12] Rockstro nickelhu Geschwul

[13] Holmqvis at coppe to conta (suppl 2

[14] Dunlap, arsenous

[15] Bailar, of a Poi (1964).

aths among
nogenic
many non-
n, many of
9]. The
ilar in
ong insec-
per smelter
The collected
rts the
mong various

are correlated
esized carcino-
port the hy-
: "...exposure
unidentified
xcessive number

>g[illegible]anch of
or[illegible]ta used
rn and B.J. Stone
s of the study
es. Also to be
ent of the
collection and

References

[1] Lee, A.M. and Fraumeni, J.F. Jr., Arsenic and respiratory cancer in man: an occupational study, J. Natl. Cancer Inst., 42: 1045-1052 (1969).

[2] Tokudome, S. and Kuratsune, M., A cohort study on mortality from cancer and other causes among workers at a metal refinery, Int. J. Cancer, 17: 310-317 (1976).

[3] Rencher, A.C., Carter, M.W., McKee, M.W., Mortality at a large western copper smelter, JOM, 19: 754-758 (1977).

[4] Pinto, S.S., Henderson, V., Enterline, P.E., Mortality experience of arsenic-exposed workers, Arch. Environ. Health, 33: 325-332 (1978).

[5] Wall, S., Survival and mortality pattern among Swedish smelter workers, Int. J. Epid., 9: 73-87 (1980).

[6] Enterline, P.E., and Marsh, G.M., Mortality studies of smelter workers, Am. J. Ind. Health, 1: 251-259 (1980).

[7] Lubin, J.H., Pottern, L.M., Blot, W.J., Tokudome, S., Stone, B.J., and Fraumeni, J.F., Jr., Respiratory cancer among copper smelter workers: recent mortality statistics, JOM, 23: 779-784 (1981).

[8] World Health Organization, Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, (Geneva: World Health Organization, 1967).

[9] Cutler, S.J., and Ederer, F., Maximum utilization of the life table method in analyzing survival, J. Chronic Dis, 8: 699-712 (1958).

[10] Munson, R.R., Analysis of relative survival and proportional mortality, Computers and Biomedical Research, 7: 325-332 (1974).

[11] Hendricks, R.V., and Archer, V.E., Unpublished data.

[12] Rockstroh, H., Zur atiologie des bronchialkrebses in arsenverarbeitenden nickelhutten: beitrag zur syncarcinogenese des berufskrebses, Arch. Geschwulstforsch, 14: 151-162 (1959).

[13] Holmqvist, I., Occupational arsenical dermatitis; study among employees at copper ore smelting work including investigations of skin reactions to contact with arsenic compounds, Acta Dermatovener (Stockholm) 31 (suppl 26): 1-214 (1951).

[14] Dunlap, L.G., Perforations of the nasal septum due to inhalation of arsenous oxid, JAMA, 76: 568-569 (1921).

[15] Bailar, J.C. III, and Ederer, F., Significance factors for the ratio of a Poisson variable to its expectation, Biometrics, 20: 639-643 (1964).

[16] Report of the Surgeon General: The Health Consequences of Smoking, U.S. Department of Health, Education, and Welfare, Publication No. (HSM) 72-7516, Washington, D.C., U.S. Govt Printing Office (1972).

[17] Welch, K., Personal communication.

[18] Ott, M.G., Holder, B.B., Gordon, H.G., Respiratory cancer and occupational exposure to arsenicals, Arch. Environ, Health, 29: 250-255 (1974).

[19] Mabuchi, K., Lilienfeld, A.M., Snell, L.M., Lung cancer among pesticide workers exposed to inorganic arsenicals, Arch. Environ. Health, 34: 312-320 (1979).

E. P. I
data that a
frequently
that was no
which I thi
relationshi
striking st
cide plant
and Lilienf
These data
retired wor
severe an e
tral Europe
and where a
excess has
to a causal
pounds are
panel to ad
based on a
forms of th
factors whi

Another
ditions in
ing water,
for the fie
going to be
actual expo
the various
given that
remain ques
perhaps hal
the dose-re

I woul
that the de
time after
experience,
it would be
pational ca

P. E. I
that there
workers. I
to look at

Smoking,
tion No.
(1972).

and occu-
: 250-255

ong pesticide
alth, 34:

DISCUSSION

E. P. Radford: I think you've seen some evidence from the human data that arsenic may not be a pure carcinogen, in the sense that we frequently think of it as an initiator. I'd like to point out something that was not emphasized today except in Dr. Lee-Feldstein's Table 5, which I think bears some repetition. It isn't only in smelters where a relationship of human cancer to arsenic has been shown. One of the most striking studies wasn't even on her slide. I'm referring to the pesticide plant in Baltimore, Maryland, which was studied by Baetjer, Levin and Lilienfeld, which has never been published in the open literature. These data were very impressive. Roughly half of a small group of the retired workers from that plant died of lung cancer, which is about as severe an epidemic as we've seen, except for the uranium miners in Central Europe. The point is that where arsenic exposures have occurred and where adequate checks on cases of lung cancer have been made, an excess has generally been found. This fact adds considerable strength to a causal relationship, but does not indicate whether arsenic compounds are carcinogens or promoters. One of the points I would like the panel to address is the question of the strength of evidence on arsenic, based on a number of different types of exposure, different chemical forms of the agent, and the presence or absence of other confounding factors which might modify the dose-response.

Another general comment I would like to make is that exposure conditions in these various populations, except possibly those from drinking water, are very difficult to obtain quantitatively. I submit, that for the field of arsenic carcinogenesis to be carried forward, it is going to be necessary to get much more quantitative information on actual exposure conditions. I think the efforts that have been made and the various studies are excellent. They are the best one can expect given that they are retrospective studies. Unfortunately, they still remain questionable. Thus, even though in the case of arsenic we have perhaps half a dozen really good quantitative studies of the effects, the dose-response relationship still remains somewhat obscure.

I would like to ask Dr. Enterline a question. Does he really think that the decrease in the relative risk of lung cancer as a function of time after arsenic exposure ceased, or the termination of the work experience, is a statistically significant change? Because if it is, it would be quite contrary to the situation that we see with other occupational carcinogens, such as asbestos or ionizing radiation.

P. E. Enterline: I think the answer is yes. I really believe that there is a decline with time in the relative risk among exposed workers. I say that for three reasons. First, in my study, if you were to look at the people exposed for five years, you'd see that the peak

SMR occurred roughly ten years after the midpoint of that five-year exposure and thereafter dropped. Secondly, this shows up in the earlier retirees' study. For men as they grew older and after exposure ceased, the SMR dropped rather sharply. And finally, there is a paper (Brown, C.C., and Chu, K.C. "Implications of the Multistage Theory of Carcinogenesis Applied to Occupational Arsenic Exposure." Submitted for publication) that analyzes the same data that Dr. Anna Lee-Feldstein presented that shows the same thing. Dr. Lee-Feldstein has not looked at it in that way. I think that this is unlike most of the carcinogens that I know about, but like radiation-induced leukemia, it does show a decline in risk as the time since last exposure increases.

E. P. Radford: That's true for radiation-induced leukemia, but not for lung cancer.

S. Lamm: Dr. Enterline, I'd like to follow up on your answer and to suggest another area where we ought to look for similarity. One area where we've had tremendous experience has been looking at the leukemias associated with benzene exposure. Benzene and arsenic are the two occupational carcinogenic exposures for which there is considerable multiple evidence of an effect in humans, but which has not been demonstrated in any other animals; therefore, it may be a species-specific effect.

We've found an interesting similar story in the benzene exposure/leukemia relationship--after exposure, the risk of leukemia seems to go down quite markedly. I think that if you look at almost any of the benzene/leukemia studies, you find that 80% of the leukemias occur within the two years after the final exposure. That is not true for most of the other types of cancer studies that we have looked at. This might suggest that with arsenic and benzene, we're dealing with a different pathological process and that possibly the types of toxicological studies we need for investigating such processes would be different from the standard carcinogenic rat-type studies.

P. E. Enterline: I think that's an interesting analogy.

S. A. Peoples: The differences I see in the studies between the people who drank the water in Utah and the exposure in a smelter is the nature of the arsenic. I've analyzed water found in Utah and in many places in Nevada where they have levels of 100 parts per billion or better of arsenic and it's all pentavalent. I'm pretty sure that if you analyze the arsenic in a smelter, you'll find it's probably trivalent.

J. W. Southwick: Dr. Irgolic will make a presentation tomorrow that will describe this in more detail. According to his data, approximately 86% of the arsenic in waters of our study communities was the arsenate (pentavalent).

M. L. Roy: I'd like to ask Dr. Southwick, do you have data on mortality in the two Utah towns?

J. W. Sc
the prelimina
interesting t
attempted to
at for mortal
arsenic-expos
tality. Howe
due to the fa
to live longe
with the 70,

M. L. Ro
cancer?

J. W. Sc
variety.

L. J. Go
can produce a
nothing about
effects due t
these other e

E. P. Ra
out that ther
levels; acute
week ago, as
call from a m
sad case of h
the arsenic i
nitely elevat
neuropathy; y
Leonard Goldw
people who ar
think, to col
not readily i

P. E. En
mination of e
death rate.
rate, but thi
dure. Men we
sons and, the
health proble
five and ten
terminations
period immedi
vious--one wa
looking at a
one of the re
population be
don't think h

J. W. Southwick: Yes, although I'm really not prepared to share the preliminary data that we have on mortality. I think it would be interesting to the group just to give a hint of what we've seen. We attempted to choose a number of communities in Utah that we could look at for mortality due to different diseases including cancer. In our arsenic-exposed community there was an apparent excess of cancer mortality. However, when you looked at the data closely, that excess was due to the fact that the people in the arsenic-exposed community tended to live longer than the others and most of the cancer was associated with the 70, 80, and 90-year-olds.

M. L. Roy: But did you notice an excess of a particular type of cancer?

J. W. Southwick: No, the cancers were of the whole garden variety.

L. J. Goldwater: I suspect that occupational exposure to arsenic can produce adverse effects other than cancer. I have heard practically nothing about either acute or chronic, systemic effects or even local effects due to occupational exposures. I wonder if anybody has studied these other effects.

E. P. Radford: I was going to introduce this session by pointing out that there are well-known effects of arsenic that occur at high levels; acute arsenic poisoning which we tend to forget about. Just a week ago, as a result of my name being on this symposium, I received a call from a man who lives not very far from here who told me about the sad case of his wife having had acute arsenic poisoning. The source of the arsenic is unknown to this day. It was a classic case with definitely elevated urinary and hair arsenic with residual sleeve and glove neuropathy; you can read about the whole syndrome in textbooks. Perhaps Leonard Goldwater's question could be amplified to say that if there are people who are aware of these isolated cases, it would be important, I think, to collect them, because apparently there are sources of arsenic not readily identified but sufficient to give serious effects.

P. E. Enterline: It should be noted that five years after termination of exposure for the men in that smelter, there was a very high death rate. Now I haven't looked at all the reasons for this high death rate, but this is one of the things that confuses the analytic procedure. Men were terminating from the smelter apparently for health reasons and, therefore, not working very long. In other words, these health problems seem to be showing up early in their worklives, after five and ten years. I think that it would be worth looking at why these terminations were taking place and why the death rate was so high in the period immediately after the termination. It could be simply the obvious--one way to terminate is to become ill or die. However, when looking at a set of data by length of exposure, you have to realize that one of the reasons exposure is short is that people are removed from the population because of poor health. This is an aspect of the data that I don't think has been thought about very carefully.

E. P. Radford: One of the things that impressed me about Dr. Lee-Feldstein's data is that the SMRs, particularly cardiovascular, were so high. Do you have any thoughts on that, Anna?

A. Lee-Feldstein: I really don't have anything to add to what I said before about heart disease. I did want to mention that there is also some indication of excess mortality from respiratory diseases, other than cancer; and there is some excess mortality due to mental disorders.

W. L. Marcus: There is an animal model published in 1979 by Maltoni and Scartino which showed that not only did benzene produce leukemia, but the animals got solid tumors of the zymbal gland as a result of the exposure. Maltoni has a history of doing very unusual experiments, but when they're repeated, they turn out to be correct. There are two other studies I'd like to mention--the Antafagusta Study in Chile and the Taiwan Study. The data that we have show, in fact, lesions called cancer seem to miraculously disappear within a year after the successful treatment of the water. The Taiwan Study, which included an enormous number of people, also showed a dose-related effect from a flourescent compound, as well as arsenic. We sent Dr. Chie Wu, a native Chinese, to talk to the person that developed this data. Dr. Wu was told that alkaloids produced peripheral vascular contraction. Arsenic also has that capacity, though to a very minor extent. This would, therefore, explain the so-called Black Foot Disease. I bring this up in relation to the Water Quality Criteria Document. I wrote numerous times to Dr. Albert explaining the flaws of the experiments he was using to determine those numbers. We pointed out the experimental problems item for item and they chose to ignore them. The Water Quality Criteria Document refers to about 22 nanograms/liter in drinking water. If the water quality criteria number were correct, Dr. Southwick's study would have produced a larger number of effects.

A. P. Borgias: Dr. Enterline, I was wondering how you felt about the validity of urinary arsenic concentrations as a measure of worker exposure and do you have any other suggestions for an alternative analytical technique?

P. E. Enterline: Initially, the reason we used the urinary arsenic as a measure was because of the protective clothing and the fact that workers were supposed to wear a mask in certain areas and in some areas I think they did. Therefore, atmospheric arsenic might not have been a good measure of the biologic intake of arsenic. There is a small study of 24 men who did not wear a mask but wore a personal sampler, and who had daily urinary arsenics. The airborne measure and the urinary measure had a correlation coefficient of 0.5. (It isn't large, but there must have been some errors in the two measurements, and at least it was in the right direction.)

A. Lee-Feldstein: An additional reference (19) is a study from northern Sweden of lung, liver and kidney tissue from deceased smelter

workers. Cop
found to have
tissue when c
kilometers aw
environment.

I. Hardi
that practical
tion. This i
we're exposed
on the log-no
didn't do thi

S. Lamm:
Criteria Docu
try to go thr
of an arsenic
Criteria Docu
occur annuall
When the calc
tumor for the
oped within t
peting risks c

Another f
daily intake o
considered the
ber did you us

J. W. Sou
more. Average
consumption da
ligrams of ars
Document assum
would not exce
arsenic exposu
adopted in the
live a long ti

S. L. Mal
gallium-arseni
arsine. Would
handling arsin
Frequently the
under vacuum c
where I work a

I. Hardin
tried to monit
measured high
eaten seafood.

workers. Copper smelter workers who had been exposed to arsenic were found to have seven times the amount of arsenic present in the lung tissue when compared with the lung tissue of men who lived some fifty kilometers away, where there was comparatively little arsenic in the environment.

I. Harding-Barlow: When you analyze lung tissue, you will find that practically all the pollutants are present in very high concentration. This is because the lungs try to filter out the pollutants that we're exposed to. Therefore, you have to compare concentration levels on the log-normal basis and I'm surprised the Swedish investigators didn't do this.

S. Lamm: Dr. Southwick, reference was made to the Water Quality Criteria Document and its risk analysis for skin cancer. While I won't try to go through a risk analysis here, one must consider the likelihood of an arsenic skin cancer death occurring. The Arsenic Water Quality Criteria Document concluded that three arsenic skin cancer deaths would occur annually in the U.S. from water containing 2 $\mu g/l$ of arsenic. When the calculation was made, it was found that the medium time to tumor for these cancers was 2636 years. One of the problems that developed within their model was an absence of a variable to account for competing risks of death.

Another factor that goes into the calculation is that the average daily intake of water is two liters per day. You indicated that you had considered the water intake of the individuals in your area. What number did you use?

J. W. Southwick: It was not much different, but it was slightly more. Average daily water intake was about 2.2 liters. Using our water consumption data, we calculated that the exposed group averaged 150 milligrams of arsenic from well water per person per year. The Criteria Document assumed that arsenic at 0.05 milligrams per liter of water would not exceed 36.5 milligrams of arsenic per year. Thus, we had an arsenic exposure of 4.1 times the maximum allowed by the standard adopted in the Criteria Document. And, by the way, folks out there may live a long time, but not 300 years!

S. L. Malish: In the semiconductor industry, many kilos of gallium-arsenide are now being used. The gallium-arsenide is made from arsine. Would it be worthwhile, to biologically monitor the people handling arsine, which is obviously very toxic, and the gallium-arsenide? Frequently the manufacture of gallium-arsenide is done under hoods and under vacuum chambers and things of that nature, but the scientists where I work are somewhat concerned about the health aspects.

I. Harding-Barlow: Some of the semiconductor companies have tried to monitor arsenic in urine of workers. The only times they measured high concentrations of total arsenic were when the workers had eaten seafood.

E. P. Radford: These were arsine-exposed workers?

I. Harding-Barlow: This was for the type of exposure that is seen in the electronics industry.

E. P. Radford: That might imply then that arsine is so toxic in its own right that you're not likely to see any arsenic effects as such.

S. A. Peoples: Arsine has a completely different type of toxicity affecting the red cells and causing anemia. Of course, one could measure the arsenic concentration in the urine, but if there are any reasonable amounts of arsine absorbed by the workers, they would be quite ill and the poisoning would be more easily detected than poisoning with trivalent or pentavalent arsenic.

A. V. Colucci: This question is for both Dr. Enterline and Dr. Lee-Feldstein. Even in the closely circumscribed atmosphere of the occupational scenario, the smelter environment is loaded with a myriad of compounds, many of which could be extremely carcinogenic. To what extent did you, could you, or would you be able to disentangle those competing factors?

A. Lee-Feldstein: We looked at sulfur dioxide separately as an exposure variable in the original paper, and we found that we didn't see the nice neat gradient in respiratory cancer mortality relative to level of SO_2 exposure that we did see in relating respiratory cancer mortality to arsenic exposure. It is difficult to separate the effects of arsenic and SO_2 in this study group, since many work areas with heavy or medium arsenic exposure also afford medium or heavy exposure to SO_2. We concluded in the original paper that arsenic, perhaps in interaction with SO_2 and other unidentified chemicals in the environment, is responsible for the excess in respiratory cancer deaths. My present information does not contradict that conclusion.

A. V. Colucci: The arsenic is associated with particulate matter and SO_2 is a gaseous component. Since the particulate matter has a number of chemicals in it, have you been able to analytically separate what these materials are and run similar correlations on other chemicals which should follow similar gradings?

E. P. Radford: Well, if they're intimately associated with the arsenic, that is, there is always a one-to-one correspondence between the arsenic level and the particulates, you're bound to get the same correlation. There are new techniques available by which if you have differential exposures to elements in the workplace, you can sort them out statistically. But if there's a one-to-one correspondence, there's nothing you can do. This was one reason why I stressed that in the pesticide plants and in the smelters an effect on lung cancer can be seen. I think the case for arsenic can be strengthened if we can eventually get quantitative dose response data and show that they are the

same regardless of all the other things that might or might not be in the same environment.

P. E. Enterline: I just wanted to add that other substances such as nickel subsulfide (Ni_2S) cause cancer. Smelters generally have higher death rates than you might anticipate, and it's hard to look at all the different kinds of smelters and connect them with a single substance like arsenic. There must be a lot of things going on in smelters that we haven't even tried to measure.

F. H. Nielsen: The studies by Lee-Feldstein show that many workers exhibited respiratory disorders. This indicates that lung physiology has been altered, probably by materials other than arsenic. Perhaps the elevation in lung and respiratory disorders can be more closely correlated with something like particulate matter. Furthermore, if particulate matter is present, the particulates may contain some unidentified carcinogenic material, for example, nickel subsulfide. Perhaps some workers are also exposed to other carcinogens like nickel carbonyl. Thus, one must be careful not to relate any increase in cancer appearance to just one agent such as arsenic. Also, I think this is another example of trying to incriminate arsenic in a variety of types of cancer without any consideration to its form or route of administration.

P. E. Enterline: I thought one interesting thing about Anna Lee-Feldstein's presentation was the fact that emphysema seemed to be increased in people with short exposures. If it's something in the general environment, you would expect duration of exposure would somehow be related to this effect.

E. P. Radford: In a symposium we had in Pittsburgh about two years ago, Dr. Marvin Schneiderman pointed out that the short-timers may be the heavily exposed ones who have done the dirty jobs. That may be one reason they leave that particular work early.

P. Mastradone: My comment deals with Dr. Lee-Feldstein's data. I was thinking that the data on emphysema tends to show--at least it has in the past--an association with exposure to aerial particulate matter. I was wondering just how much you thought subtracting that kind of data out of your lung cancer assessment situation might show arsenic to be considered a carcinogen?

A. Lee-Feldstein: I have not yet looked at that for this follow-up study. We originally had some data on other agents such as silica, lead fumes, and ferromanganese dust, and I really feel that the other agents that had been measured in the atmosphere (other than SO_2) were not strongly implicated. However, we didn't make a formal attempt to "subtract them out." We had the same kind of problem that we have with sulfur dioxide: the exposure to these various agents was simultaneous.

P. Mastradone: My idea is that something similar to silicosis might be occurring where you get constant irritation of the lung lining. It seems to me that this would have a tendency to promote cancer of the lung.

A. Lee-Feldstein: In fact, Lee and Fraumeni found that excess respiratory cancer mortality was inversely related to degree of exposure to silica, which seems to contradict your theory, at least as far as silica is concerned.

E. P. Radford: Apropos to that comment, there is no evidence of a synergistic effect of silicosis or chronic lung disease and radiation-induced lung cancer.

J. W. Southwick: I'd like to respond to the oft-stated comment of "why worry about the Drinking Water standard for arsenic?" The reason is that excess arsenic in water violates regulations. That's why you worry about it. And, to give you a follow-up on our study community, as soon as we had submitted our report to the research branch of EPA showing no observed health effects, the enforcement branch of EPA descended on the community of Hinkley and said, "You can't have water with arsenic at this level; it's in violation of the standard." And they said, "Well, we don't have any money to do differently." EPA essentially said, "That doesn't count. You still have to correct the problem. Our regulations don't allow you to have a public drinking water system the way it is." So the town applied for a federal grant to correct the problem, and the last I checked on it, I think they were in the mill for almost a million dollar grant to correct the problem EPA said they had.

C. Gordon: Dr. Enterline, in your 1977 update of the Tacoma Study, you said that pre-1950 exposures were five to ten times the 1973 exposures. However, on the chart (Table 7) which showed exposure pre-1950, '50s to '60s, '60s to '70s, and post-'70, which I presume is the '73 data, it looked like the general differential between pre-1950 and 1973 was by a factor of about two, not five to ten. I was wondering if you had any comment on that.

P. E. Enterline: I think that was a statement that Sherman Pinto put in the paper, and I assumed that he knew something more than is on the chart there. I do know that the air data we have that goes back to 1937 shows extremely high levels in the 1930s and so perhaps he was referring to air concentrations and made some kind of estimate. But you're absolutely right. The chart shows about a doubling and the paper does have a statement in it as you say.

I. Harding-Barlow: Your Table 2 showed urine levels but without a 45° slope.

P. E. Enterline: That's right. I think the urinary arsenic levels were about double around 1950, compared with 1973.

I. Har
air because
one-to-two

P. E.

C. Gor
airborne ex
study, Dr.
was at a ch
had any com

P. E.
with crude
for all thr

I. Har
three studi
p value of
air, food,
one assesse
verts it to
differences
assessed an

E. P.

I. Har
air and wat

M. Sch
estimates?

I. Har
extremely h

E. P.
to see the
concentrati

E. A.
sis as a me
the arsenic
urine as ei
to confuse
bly most of
grown on hi
arsenic. I
cussed in g
pesticide p
efficacy, f

I. Harding-Barlow: But this doesn't mean anything with regard to air because you do not have a 45° slope. Therefore, you do not have a one-to-two correlation between urine and the air.

P. E. Enterline: Yes, that's right.

C. Gordon: In May, 1980, EPA published a risk assessment for airborne exposure to arsenic making use of Dr. Enterline's original study, Dr. Lee-Feldstein's original study and the Baltimore study, which was at a chemical plant. I was wondering whether any of the panelists had any comments on the EPA risk assessment.

P. E. Enterline: I've seen it. The amazing thing is that even with crude wild methods, it came out with about the same kind of answer for all three studies. I should add it's pretty ingenious.

I. Harding-Barlow: I would like to point out that using these three studies and the EPA extrapolation techniques, one comes up with a p value of ten to the minus two, for the air equivalency of our normal air, food, and water exposure to arsenic. As explained in my paper, if one assesses normal intake of arsenic from food, air, and water and converts it to an air equivalency by making the proper assumptions as to differences in percentages absorbed, et cetera, a value for p can be assessed and it is approximately 10^{-2}.

E. P. Radford: How can you equate that to inhaled arsenic?

I. Harding-Barlow: The details are given in my paper both for air and water equivalencies and lung and skin cancer probability risks.

M. Schneiderman: What are the confidence limits on these estimates?

I. Harding-Barlow: Even at plus or minus 50%, this is still an extremely high lifetime probability risk.

E. P. Radford: I for one would feel that it would be necessary to see the calculations by which you go from food levels to airborne concentrations before one can assess their equivalence.

E. A. Woolson: Just to make three quick points. Using urinalysis as a measure of industrial exposure is fine, as long as you speciate the arsenic. If you're exposed industrially, it'll be present in the urine as either arsenate, arsenite, or cacodylic acid. You don't want to confuse the arsenic compounds you get from eating seafood and probably most of your other food. Most of the arsenic in vegetable crops grown on high arsenic soils, for instance, is not there as inorganic arsenic. It's as an organic complex: It will hydrolyze. This is discussed in greater detail in my presentation. Secondly, the Baltimore pesticide plant which utilized lead and calcium arsenates, to improve efficacy, frequently used lime sulfur as an adjuvant. I've done some

studies with lime sulfur and it causes a reduction of some of the arsenate to arsenite. Therefore, they had exposure to copper, a wide variety of sulfur, oxisulfur compounds and sulfides, as well as lead and calcium arsenate. In terms of arsenic essentiality, we've seen it many times in plant studies where we grow plants on low arsenic containing soils and add, as a treatment, a variety of arsenic levels. We do get a stimulation in growth and yield at low arsenic levels. Again, maybe this is an indication of essentiality for plants. We've not analyzed it on a statistical basis, so we can't really say anything about it definitely, but it is an indication.

W. L. Marcus: I'd like to talk more about a study of the ASARCO plant. As part of a thesis, Dr. Genevieve Matanoski did a study funded by EPA. She used census tracts and interviews with the people in those areas to determine mortality. Dr. Matanoski, in looking at mortality records, was able to show that as people lived farther away from the plant there was a decrease in the number of lung cancers. As I recall, at our request she obtained soil samples near the homes and was trying to correlate the levels of arsenic in the soil samples as a measure of exposure in relationship to distance from the plant.

E. P. Radford: I'm familiar with Dr. Matanoski's study, because I was involved in the inception of it. It is true that that census tract had a high lung cancer rate which was one of the reasons why the arsenic connection was investigated. But I think the recent report published by Dr. Matanoski ("Cancer Mortality in an Industrial Area of Baltimore," Matanoski, G., Landau, E., Tonascia, J., et al., in Environmental Research, Vol. XXV, pp. 8-28. Academic Press, 1981) indicates that there is not a clear relationship between the proximity of the plant and the high incidence of lung cancer. There was a possibility that the freight cars bringing in arsenic trioxide might have dribbled small amounts near the plant. But I don't think that the connection between arsenic and lung cancer is clear cut at all.

W. L. Marcus: I want to make a second point to Dr. Southwick since my office sets regulations for drinking water. We are looking very seriously at raising the allowable arsenic levels. Those levels were originally set, as were most of the MCLs, in 1964 by the United States Public Health Service. For many of them there was not a clear reason for the numbers they chose. There are towns in the United States with very high levels of arsenic, including Fairbanks, Alaska, where the drinking water has levels similar to those presented by Dr. Southwick or a little higher, in which there was no evidence of increased mortality or cancer. So we're very seriously considering raising the level although I don't know by how much. The reason the enforcement people became involved is because that is the way the law reads. If you exceed the level, they have very little choice. However, under the Variance and Exception Provisions, you could have applied for a variance and received it for at least two years.

J. W.
community o
community o
exemption b
its own pri
tion, and o
money in De
This has a
going in an
painful thi
spend a mil
standard is

J. W. Southwick: An exemption was applied for and granted to the community of Hinkley for its public water system. The unincorporated community of Deseret had no mechanism for getting a variance or an exemption because they did not have a public water system (each home had its own private well). As a consequence, the Farmers' Home Administration, and others who loan money for home construction, refused to loan money in Deseret because there was no variance or exemption granted. This has a tremendous economic impact because a large power plant is going in and the area anticipates a big development boom, so it's a very painful thing for them. Not only is our government possibly going to spend a million dollars to "improve" that water system, but its arsenic standard is having a dramatic economic impact on these small communities.