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~~Washington Office~~

Vinyl chloride

Vinyl chloride - ORC Washington Nelson 3/18/80

Joe Seawell Neoplasms 23 mos lung

T1 male 14

T2 " 30 female 31 lung (mostly metastatic from liver)

T3 " 36 " 41

T4 " 36 " 36

Brain 23 mos

Animals 664, 667, 672 male rats T3

Off by sheet

T2 1

Buery

T3 3

By 19 23 mo. report

~~Male rats~~

Female rats - no brain tumors

Male mice " " "

female " " " "

Kidney several other tissues

T3, T4

Do not discuss legal advice obtained. Facts OK.

Purpose to let us know why Carbide decided to release them & interim report was delivered to govt. agencies after 800 set up.

1978 Audit report

Issue accountability prob.

Buery issued pathology report July, 1978

T3 Only looked at 6 brains - 3 brain tumors - 23 brains saved

T2 males 22 and 18 examined mice. 1 brain tumor.

Did not look at microscopic slides. Brain tumors - neuroepithelioma (primary)
0-3% normal in this strain.

Bussey did spot check of histopathology & found correct.

Early Jan. 1979. Audit task group met with Dr. Bussey.
accepted his Jan. 9 report.

Recommended that because of lack of tissues no further pathology be done.

Texas city then took center stage.

Dr. Bussey recommended further pathology be done on animal reports. Of the 23 brains available had only looked at 6 (3 tumors)

36 had proposed that a compilation of tissues be made so a list could be submitted for estimate of cost.

Became involved in trying to recover funds. - Sept.

Found current atty for Palace now pres. of IBT.

Concluded couldn't sue realistically because bankrupt.

Not relevant to data issues.

Had recommendations by audit comm. which have not been followed up.

Carbide decision not crystallized yet whether to put into 8c.

Joe Wagoner was heard on a plane to say "I've finally got the piece of evidence which will sink CMA on VC". Maury Johnson thinks was one of Goodrich cases which they settled responsibly.

Many Minetti. Carbide lawyers who come into review date.

Hutt - Counsel on 8c. Two issues.

- ① Distribution of Bussey report. Recommendations give as follow-up to govt. agencies. For key. Promptly because of brain tumors (3 of 6 examined).

Advises that we draft this afternoon. Send tomorrow.

(2) Treatment & distribution of IBT data & Tissues

Recommends look at the brain data & tissues if still available. ^{Peter} Hutt felt strongly should do.

(Hutt lawyer at Covington & Burlington counsel for CMA on TSCA matters)

Whelan - no connection @ Dupes City with VC.

Voted to send to the 6 govt. agencies. (1) above

② Reading other brain tissues

23 brain tissues in T3 category 6 of which have been ^{used} in Table I. Were 25 animals. 23 saved.

Others probably discarded because decomposed.

Originally Dr. Busey said "no further pathology"

In light of Dupes City later recommended that it would be wise to review other brains.

Busey thinks should look at all brains.

On 1 mo & < 5000 to look @ 270 tissues.

URL 15995

Moved that we look at all available brain tissues in the entire study.

5. Termination of Ind. Bio. Test -

Doesn't think wise to buy current right now. Will try to get ^{some} Will not pay less 5%.

In general study was a disaster. The only reason we're going ahead is because it was recommended to do a yr. ago.

Current has said not throwing away any tissues.

Recommended we advise at termination of availability of tissues for 6 mo. At end of 6 mo we wash our hands.

NIN Conference 3-26-21/86 Vinyl chloride
OSHA, ~~OSHA~~, NIN, NIEHS Bethesda, Md.

Maltoni - most extensive study of an ind. exp. in carcinogenesis

Different species strains sex

Rat Morris Hamster

Rat Sprague-Dawley Swiss mice
Wistar

Golden Hamster

M-F

Adult

4 Routes

Inhalation

Injection - intraperitoneal

" subcutaneous

Oral

Extremely complete, detailed, careful.

700 animals.

Report in process. Available in a few weeks.

This work will be the definitive study.

Results - Rats & dogs inhalation 50,000 - 1 ppm.

1st 10,000 - 50 ppm multi tumors.

50 ppm - still active variety

2 5, 10, 1 ppm. 25 ppm active. Mammary not dose related

17 rats - some types less sensitive to tumor.

100 days of treatment scattered different groups 10,000 & 6,000?

Length of - important.

Effect of age - young more sensitive
Sprague ^{Wistar} ~~Dawley~~ rats males

30,000 Swiss mice 10,000 - 50 ppm

Don't 250 ppm - lower lung height

Considerable species differences

Sprague Dawley 30,000 - 1 ppm inhaled

10 ppm lower limit. Some types only at high dose.

Feeding ca 0.3 mg/kg.

Sprague Dawley more sensitive than Wistar

Newborn much more sensitive

Conclusions

10 lowest active dose inhaled.

0.3 mg/kg oral

Did have mammary tumors at low dose but not dose related.

Paper Luzak & Mc. Sincel

Seems to show pulmonary tumors at 1 ppm 10/group.
Dose related.

Dr. Zambare - also found pulmonary increase among workers

but not dose related among workers. Doesn't seem to relate to it.

Smith - NIOSH

Age susceptibility - interested only in mature animals.

6, 18, 38, 58 wks. 110-125/gp.

Exposure ended after 28 wks - was sufficient.

Autopsied some 3, 6, 9 mos after start exp.

No hematological or clinical differences

Liver angios, pituitaries, lung

1st angio 16 wks.

Actually in males oldest had highest angio

Also more metastasis for older

Time to 1st diagnosis shorter in older

Females more susceptible

Produce - Alcohol + VC (600 ppm H₂O, 5d/wk (1 yr)

5% alcohol instead of 10%

300 SD rats

Alcohol started 6 wks ahead + cont'd. for life.

Filtered air

" " + E₁ + E₂

" " + VC

" " + VC + E₁ + E₂

Combinations more carcinogenic

Diagrams 3 VC alone.

Increased tumors with combinations

Even E₁ + E₂ alone increased tumors

1. Should collect good alcohol consumption data.

Helin - GPSC

1. Cancer seems dependent on total dose
2. Dose suff if high enough
- 3.
- 4.
5. Mice more carc than rats

Griffith - Pneumoniosis of PVC

Less 121 0.5 - 0.1 μ

13 mg / M³

Also analyzed for VC

80 rats, 10 guinea pigs, 10 monkeys

Mean exp 13 mg / M³ rats

exp 10.4 mg / M³

VC in monomer 0.01 - 0.02 ppm

Design - pulmonary function tests in monkeys

Rats - auto collections of macrophages in lungs

Monkeys - pneumoniosis less in rats & guinea pig

PVC dust is respirable, can be identified, no pulmonary difficulty after 13 mo. Benign

Wagner - Intrapleural

Particles < 1 μ m injections

In lat experiment $\rightarrow$ liver tumors. Haven't reproduced it.

Inhalation

Stays in lung. Do get some in Kupfer cells of liver.

Maltoni - Spectrum cytology

Included " " in ship exams of all VC & PVC workers in Italy.

3350 workers examined

Does find effect on PVC workers.

Seems to be in cigarette smokers.

Distribution in spleen & liver - may be transported by macrophages.

Angiosarcoma is of endothelial origin. } Wagner says no evidence of cancer.

If in macrophages no problem.

Truth - seems to be an inert dust - some reaction

Not inert in sense some people think

Is there & there is a reaction to it.

Will publish proceedings in Environ Health Perspectives
Infantile testes

Liver, Biliary, Pancreas, digestive

A no. of studies show brain cancer X's

Respiratory - generally high.

Concludes brain, lung & possibly lymphatic-hematopoietic system may be target organs.

Weber -

VC workers
In study most SMR as low as VC PVC workers

SMR high for Lymphatic & hematopoietic, GI tract, liver
Ischemic hearts, tumors-brain

Cooper — Not convinced brain tumors related to VCM
but seems to be a problem in the industry.
Power — probability of detecting an error that exists

Dale — Angiosarcoma

1964-1974 tried to find all cases by various means

168 cases hepatic angiosarcoma. Only 74 recorded.

Pathologists best source. Most as listed not correct.

127 male 155 white

41 female 13 non white

angiosarcoma cases peak ca 45 yrs. 50-59 yrs.

Male Female

VC 12

Thorax 15

AS 4

Endocrine
metabolic
diseases 3

Last used 1955. Have been increasing. Latency lengthening.

Prober's film no longer used.

Idiopathic somewhat later older.

0.75 people / 10MM / yr.

Highest rates in NE. May be under reporting in rural areas.

Thinks may be other chemicals which cause AS.

Rafter — HBR 1962-1977

Liver function tests not a good way to detect early

Jamburro

1200 w/ phas
med screen
A. History

B. Physical

Burden

Prog

IGG Test 1st

Alkaline phosphatase 2nd

Other fed reg. meaningless

Jones reported on the Studies in 1974-1977

No new data. Weren't greatly worried re dust in '74.

3/24/80

Chiazzi. Did report on follow-up study.

4938 deaths 64-73

3847 " among whites actually reported on.

No significant risks

Molina - PVC Fabrications Sweden

Retrospective mortality Does 6 mo exposure

1945 thru '74

Exposure

High - Exposed in mixing

Med - Nerves in mixing but handling warm PVC

Low - " where warm PVC was handled.

1970 persons Sweden has death Tapes on all persons dying in Sweden

Results:

① Young group < 30 yrs of age at beginning 1500 had exp

2

3 112 Highly exposed

Found 14 malignant cases vs 11

Myocardial infarction 15 vs 10

URL 16002

Long exposure

No increase in deaths

Myocardial infarctions high. Thinks phys. act. & smoking imp. factors.

Tumors - largely gastrointestinal

Section

Questions

1. Rel. exp.

2. Does dust exp. relate to x-ray ch

3.

4.

Studied entire workforce since 1967.

2308 Couldn't study all samples.

Had 819. Got most of those most exposed to dust.

NR questionnaire tried all jobs

FEV₁ & FVC

TLC & TLC in 1/3 of sample

PA Chest x-ray

Samples respirable dust

Developed a dust index for each. Good relative exp. in different jobs.

Found a loss of breathing cap. related to dust exp.

No evidence of loss of diffusing cap. with dust exposure.

Radiological - not easy.

Have found a pneumoniosis with small loss of respiratory cap.

Related to P/C dust.

Martinez - a small relationship with PDC dust

Chapman - Louisville

X S Cancer

Lung cancer 42 to 28

Only Adenocarcinoma and large cell undifferentiated cell types
excess.

Chem. Co. rated for exposure to 19 chemicals

showed strong correlation between PDC dust & above 2 types

Leis - DDE Linai

Studied 3 plants

Long time exposure - most over 10 yrs.

Usually started in logging then moved to polymerization and

could not distinguish between VC & PVC

Due to physical layout no pure exp.

Abnormal Chest X-Ray

Plant	F	No	%
A	290	66	22.7
B	250	46	19.4
C	445	19	4.3

exposure well controlled type

Studied 1st 2 plants further

significant relationship between abnormal chest X-rays
& smoking.

Granulomatous followed by fibrosis

Some data that VC cannot be completely excluded as causes

Ranked vs 21 chemicals

Lung cancer not related to PVC

" " cases tended not to relate to any of the chemicals

Rice N-er nitrosamines

Fetus may be more susceptible

" have different types of cancer

Exposure up to day 10 → no tumors in fetus

Considerable difference one animal species to another

Where chemical has short half life must be formed in the fetus if metabolism dependent

Many carcinogens have long half life

Bialoni found VC a transplacental carcinogen @ 6000 + 10,000 ppm

Due to chloroacetaldehyde formed by mother & transfer to fetus

Fabreconi

34,000 / 1 MM children have some congenital malformations

Ca 1 of 2 pregnancies abort

1910 - 1965

Infectious diseases down

Birth defects up

Life years lost much greater than for cancer + heart attacks

Mutagenicity of VC

Salmonella - Ames +

+ in 3 bacterial systems

Drosophila + recessive lethal

Mammalian

Metabolism in hamster cells +

Chromosomal aberrations in male rats ?

Reproduction interference -

Decrease in motility of sperm in rats ?

Human observations

- Chromosomal aberrations in mal workers +
- XS miscarriages in wives of mal workers +
- Decrease in motility & numbers of sperm in workers —

Maureen Hatch

Maltoni thinks there is a transplacental carcinogenesis with VC. Has study underway.

2:50 P.M. EPA

1st monitoring showed could be found in air around plants

Set up more careful study.

Set up 24 hr samples at carefully chosen locations 2X/week
max 24 hr.

Shell - Naco

10.6

Goodrich - Louisiana

0.32 ppm

Conoco - Aberdeen, Miss

9.2

This study to validate methods. Mostly on plant grounds
Coincident with emissions

PVC fab. plants. Picked largest

5 plants Much lower 0 - 7 ppb.

~~And more~~

~~Concussion~~

PVC plants highest

Makes point that if angiosarcoma (high in NY state) truly found,
should look for all symptoms of VC.

URL 16006

Breast

VC & VBr

10-1250 ppm 4 levels 6 hrs/day 5 days/wk 24 mos.

Examination Sacrifices 6, 12, 18 & 24 mos (all)

VBr decrease in body wt. all levels. Dose related.

Increased most 350 days 1250 days.

ca 500 d. for thurs

Increased incidence 3 neoplasms all levels

Angiosarcoma liver - dose related

Total # of animals at 3 lower levels - related to dose

Latency period - dose related

Total cancer dose related.

In females time to 1st AS not dose related.

Similar to VC. Didn't find in other organ systems

Chem NCI 6 cpts. ^{Animal} Exper

VC

Vinylidene chloride VOC Liver AS (low), mammary, kidney SD

Dichloroethylene TCE Spleen - Hepatocellular mcs, - rats

Tetra " " PCE Weak

1,2-Dichloroethene + several strains rats, mammary

1,2 " Br " + numerous Mammary, nasal

Epichlorohydrin Nasal, skin.

TCE + in mouse, - in rats.

May be an epichlorohydrin imp.

A study under way with epichlorohydrin free material.

POC May be a strain as well as species difference

Agenda

Epidemiology of VC related chemicals

Only epichlorohydrin & dry cleaning solvents high

Samples too small

TCE contained epichlorohydrin

NCE tests Technical grade materials

Zed Benzene - Ethyl

Panel

Haddis - calm, balanced approach

Wolke - OSHA spoke vehemently as Schweiker bill which would
allow 2% of workers to be seriously hurt Pushing for a stronger
OSHA

Intervention in U.S. n.g. For many ways of defensing
Suggest fine in line with cost & correct to be refunded
if correct

Murray Johnson - from standpoint of physician Doesn't have
the tools sep with cancer of the major organ system. Need
tests which will enable to find early enough to do something
about it. Believes in physicals but don't really help here.

Nicholson - Mrs. Simon

Considers VC potent carcinogen. Need follow up.

Should identify high risk individuals & give special

tests. Regardless of standard should strive to reduce to minimum

DeWagner - Argued for proper epidemiology.

Fingerprinted studies with high power

Brady et al. J. Nat'l. Cancer Inst.

5 of 10 women with AS₂ ^{in NY state} lived within 1 mi. of P/C polymerizing plant. None of course.

Stress need to keep down dust in plant & in neighborhood.

Urged reassessment of idea that P/C is a nuisance dust.

0.01 - 45

0.20

0.06

105

~~8~~

~~8~~

0.13

0.06

6 $\sqrt{0.51}$

0.095

URL 16010